

Quaternary Ammonium Salts

Their Use in Phase-Transfer Catalysis (Best Synthetic Methods)

Author: R. Alan Jones

Elsevier, 2001

ISBN: 978-0-12-389171-6

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Preface

The increase in the rate of reactions catalysed by quaternary ammonium salts is often proportional to the concentration of the catalyst used. When I started to collect data for their use in organic synthesis, it rapidly became obvious that it was difficult to make a clear distinction between purely catalytic reactions and those using stoichiometric amounts of the ammonium salt; this was because the practical techniques often varied (e.g., liquid:liquid two-phase reactions vs liquid:solid two-phase reactions). Consequently, I have presented a general practical overview of the use quaternary ammonium salts, categorised according to specific bond formations or reaction types. I have tried to be as comprehensive as possible, but in order to keep the text concise, some abstruse experimental variations have been omitted, as has a complete citation of the patent literature.

The experimental methods are edited versions of original procedures taken from the literature and have been rewritten to provide a uniformity of style. Although care has been taken to ensure that all important and relevant information has been included, consultation of the original literature is recommended, particularly where cautionary notes are included with the experimental details. In several cases, the procedures have been “generalised” and variations are recorded for the specific examples cited or in the Tables. Wherever possible, limitations of experimental procedures have been given.

I am indebted to Professor A. McKillop for introducing me many years ago to the catalytic effect of quaternary ammonium salts in organic synthesis and encouraging me to write this book. In addition, I acknowledge the help and encouragement of all members of the Faculty of Organic Chemistry at the University of East Anglia for their support of the venture. Finally, my thanks go to my wife Ann for her patience and understanding over the very many years that it has taken to produce the final manuscript.

Abbreviations

QUATERNARY AMMONIUM CATIONS

Adogen (Adogen® 464)	trialkyl(C ₈ –C ₁₀)methylammonium chloride
Aliquat (Aliquat® 336)	‘tricaprylmethylammonium chloride’
CTMA	cetyltrimethylammonium (<i>n</i> -hexadecyltrimethylammonium)
DDDMA	di- <i>n</i> -decyl(dimethyl)ammonium
DDTMA	(<i>n</i> -dodecyl)trimethylammonium
EHDA	ethyl(<i>n</i> -hexadecyl)dimethylammonium
HDTMA	<i>n</i> -hexadecyltrimethylammonium
MTOA	methyltri ‘ <i>n</i> -octyl’ ammonium (Aliquat 336 or Adogen 464)
PTMA	<i>n</i> -propyltrimethylammonium
PhTMA	phenyltrimethylammonium
TBA	tetra- <i>n</i> -butylammonium
TBBA	benzyltri- <i>n</i> -butylammonium
TBMA	tri- <i>n</i> -butylmethylammonium
TDTMA	(<i>n</i> -tetradecyl)trimethylammonium
TEA	tetraethylammonium
TEBA	benzyltriethylammonium
TEHDA	triethyl- <i>n</i> -hexadecylammonium
TEPA	triethyl- <i>n</i> -propylammonium
THA	tetra- <i>n</i> -hexylammonium
TMA	tetramethylammonium
TMBA	benzyltrimethylammonium
TOA	tetra- <i>n</i> -octylammonium
TOPA	tri- <i>n</i> -octyl- <i>n</i> -propylammonium
TPA	tetra- <i>n</i> -propylammonium

OTHER ABBREVIATIONS

AIBN	azobisisobutyronitrile
BOC	<i>t</i> -butoxycarbonyl
CAN	cerium(IV) ammonium nitrate
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulphoxide
EDTA	ethylenediaminetetraacetic acid, disodium salt
HMPA	hexamethyltriposamide
NMP	<i>N</i> -methylpyrrolidone
TDA-1	tris[2-(2-methoxyethoxy)ethyl]amine
THF	tetrahydrofuran
THP	tetrahydropyran
Tf	triflate
Tol	4-methylphenyl (4-tolyl)
Tos	4-toluenesulphonyl (4-tosyl)
TOSMIC	4-tosylmethylisocyanate

General Principles

1.1 INTRODUCTION

Organic chemists are frequently faced with synthetic routes which require the reaction of water-soluble reagents with water-insoluble organic compounds. Nucleophilic substitution reactions invariably involve the use of inorganic or organic anions, the majority of which have little or no solubility in organic solvents, and many of the commonly used oxidation reactions for organic compounds employ lipophobic inorganic oxidants. Conversely, many of the organic substrates are insoluble in water. Consequently, such reactions take place only at the interface between the organic and aqueous phases and are frequently slow or inefficient. Traditionally, this problem has been resolved by increasing the interfacial surface area by rapid stirring, or by emulsification. Alternatively, the encounter rate for the reagents can be enhanced by their dissolution in a homogeneous medium. The use of a hydroxylic solvent may still inhibit the reaction, however, owing to excessive solvation of the anionic species. In contrast, polar aprotic solvents, such as dimethyl sulphoxide, dimethylformamide, or hexamethylphosphoric triamide, which tend to solvate the cation and leave the anion unsolvated, generally provide a suitable medium for the reaction. Unfortunately, they suffer from the disadvantage of being generally expensive to use on a large scale and, as with mixed solvent systems, they are recoverable only with great difficulty in an acceptable degree of purity from the reaction system.

It was a result of demand from industry in the mid-1960s for an alternative to be found for the expensive traditional synthetic procedures that led to the evolution of phase-transfer catalysis in which hydrophilic anions could be transferred into an organic medium. Several phase-transfer catalysts are available: quaternary ammonium, phosphonium and arsonium salts, crown ethers, cryptands and polyethylene glycols. Of these, the quaternary ammonium salts are the most versatile and, compared with the crown ethers, which have many applications, they have the advantage of being relatively cheap, stable and non-toxic [1, 2]. Additionally, comparisons of the efficiencies of the various catalysts have shown that the ammonium salts are superior to the crown ethers and polyethylene glycols and comparable with the cryptands [e.g. 3, 4], which have fewer proven applications and require higher

concentrations of catalyst compared with the ammonium salts, which mitigates against their use in large-scale industrial applications. It is for these reasons that this text is confined to the utilization of quaternary ammonium salts in organic synthesis.

The quaternary ammonium cations have the ability to form essentially non-solvated electrically neutral lipophilic ion-pairs with the anionic species, which are soluble in polar and non-polar organic solvents. The general basic experimental procedures were established independently by three groups working in Sweden [5], Poland [6] and the USA [7], although Triton B (benzyltrimethylammonium hydroxide) was well established as a base for use in non-aqueous media well before the advent of phase-transfer catalysed reactions as we now know them, and several isolated examples of the use of quaternary ammonium salts to accelerate two-phase reactions were known prior to the 1960s [e.g. 8] and with patents dating to the early 1900s [e.g. 9]. The fundamental technique was initially referred to as 'extractive alkylation' or 'ion-pair extraction', but the term 'phase-transfer catalysis', which was first used by Starks in 1971 [10] is now generally accepted.

For most phase-transfer catalysed reactions, the rate-determining step is the interaction of the reactive substrate with the anionic species in the organic phase and, compared with the corresponding interfacial reaction in the absence of the catalyst, rate enhancements of 10^7 are not uncommon. The virtual absence of water from the organic phase under strongly basic liquid:liquid or solid:liquid two-phase conditions allows for the formation of water-sensitive anions, such as carbanions (Chapter 6), and obviates the need for strictly anhydrous conditions and the use of bases such as sodium hydride or sodamide, etc. The phase-transfer catalytic process consequently has lower safety risks and is environmentally more friendly.

The ammonium catalyst can also influence the reaction path and higher yields of the desired product may result, as the side reactions are eliminated. In some cases, the structure of the quaternary ammonium cation may control the product ratio with potentially tautomeric systems as, for example, with the alkylation of 2-naphthol under basic conditions. The use of tetramethylammonium bromide leads to predominant C-alkylation at the 1-position, as a result of the strong ion-pair binding of the hard quaternary ammonium cation with the hard oxy anion, whereas with the more bulky tetra-*n*-butylammonium bromide *O*-alkylation occurs, as the binding between the cation and the oxygen centre is weaker [11]. Similar effects have been observed in the alkylation of methylene ketones [e.g. 12, 13]. The stereochemistry of the Darzen's reaction and of the base-initiated formation of cyclopropanes under two-phase conditions is influenced by the presence or absence of quaternary ammonium salts [e.g. 14], whereas chiral quaternary ammonium salts are capable of influencing the enantioselectivity of several nucleophilic reactions (Chapter 12).

Quaternary ammonium salts are also known to promote nucleophilic substitution reactions in two-phase systems through the formation of micelles [15], but there is no evidence for micellar formation by bulky ammonium salts, such as tetra-*n*-butylammonium bromide, under liquid:liquid two-phase conditions [16].

Synthesis of quaternary ammonium salts [17]

A very large number of the ammonium salts are commercially available. Others can be synthesized by simple quaternization of tertiary amines [e.g. 18] and by anion exchange reactions on the commercially available salts. Simple anion exchange under liquid:liquid two-phase conditions using an aqueous solution of an inorganic salt and an organic solution of the quaternary ammonium salt [e.g. 18] depends on the relative stabilities of ion-pairs formed between the anions and the quaternary ammonium cation and upon the partition coefficients of the ion pairs between the aqueous and organic phase. Among other factors, the hydration of the anions is a critical factor in the success of the anion exchange reactions under these conditions (see Section 1.2). Because of the high hydrophilic nature of fluoride and hydrogen sulphate anions, their quaternary ammonium salts are not readily prepared by anion exchange under liquid:liquid two phase conditions (unless the more hydrophilic ammonium sulphate is used [19]). Quaternary ammonium fluorides are best obtained by titration of the corresponding ammonium hydroxide with aqueous hydrogen fluoride [e.g. 20–24], or by direct anion exchange under solid:liquid two-phase conditions [25]. The salts are hygroscopic and usually still retain water of crystallization; most commercial quaternary ammonium fluorides are available as hydrates, $R_4NF \cdot nH_2O$. It is not possible to obtain ‘anhydrous’ ammonium fluorides, which provide a source for the highly reactive ‘naked’ fluoride anion, although several claims to that effect have been made [e.g. 25–27]. Quaternary ammonium hydrogen sulphates are best prepared via the lipophilic ammonium thiocyanate [28].

Anion exchange resins are also used frequently for the synthesis of specific quaternary ammonium salts [e.g. 29].

1.1.1 Quaternary ammonium fluorides

Method A: Aqueous TBA-OH (10%, 25 ml) is titrated with aqueous HF (10%) to pH 7–8.5. The solution is cooled to 0°C and the crystalline TBA-F \cdot nH $_2$ O is collected and dried at 30–40°C over P $_2$ O $_5$ at 0.5 mm Hg to yield the almost ‘anhydrous’ TBA-F as a hygroscopic glass, which is powdered and stored over P $_2$ O $_5$.

Method B: TBA-HSO $_4$ (16.98 g, 50 mmol), KOH (3.1 g) and KF \cdot 2H $_2$ O (141.2 g, 1.5 mol) in H $_2$ O (100 ml) and PhH (500 ml) are stirred at room temperature for 1 h. The organic phase is separated and evaporated under reduced pressure and azeotropic distillation of the residue in PhH:MeCN (1 : 1) yields TBA-F \cdot 3H $_2$ O (>95%).

Method C: The quaternary ammonium chloride (23 mmol) in MeOH (40 ml) is shaken with solid KF (2.2 g) for ca. 15 min at room temperature. The mixture is filtered and a further amount of KF (2.2 g) is added and the mixture is shaken for a further 15 min. The MeOH is reduced to 75% of its volume and filtered to remove KCl. The evaporation and filtration processes are repeated three times to yield the hygroscopic ammonium fluoride (>95% containing ca. 5–10% ammonium chloride).

1.1.2 Quaternary ammonium hydrogen sulphates

The quaternary ammonium bromide (15 mmol) in CH $_2$ Cl $_2$ (50 ml) is shaken with three portions (1.2 ml) of aqueous KSCN (sat. soln, ~65 mmol). The organic phase is

separated, dried (Na_2SO_4) and evaporated under reduced pressure. The ammonium thiocyanate is taken up in H_2O (10 ml), cooled to 0°C , and an excess of conc. H_2SO_4 (ca. 20 ml) is added. The mixture is warmed to 75°C and the evolved gases are taken through aqueous NaOH (33%) and methanolic KOH (11%). When the reaction is complete, the mixture is cooled to room temperature and poured into aqueous KHSO_4 (sat. soln., 30 ml). The mixture is extracted with CH_2Cl_2 (3×15 ml) and the extracts are washed well with aqueous Na_2SO_4 (sat. soln., 3×5 ml), dried (Na_2SO_4) and evaporated to yield the quaternary ammonium hydrogen sulphate (>85%).

Because of their high lipophobic character, compared with other ammonium salts, quaternary ammonium hydroxides are not readily prepared by liquid:liquid anion exchange. Only with quaternary ammonium hydrogen sulphates is it possible to transfer the ammonium hydroxide into the organic phase in any viable degree of concentration [30] and this procedure remains the cheapest and simplest procedure. Other methods include treatment of quaternary ammonium halides with silver oxide [31] and by anion exchange using polymer bound hydroxide [e.g. 32].

The synthesis of polyhalide salts, R_4NX_n , used in electrophilic substitution reactions, are described in Chapter 2 and H-bonded complexed salts with the free acid, R_4NHX_2 , which are used for example in acid-catalysed cleavage reactions and in electrophilic addition reactions with alkenes, are often produced *in situ* [33], although the fluorides are obtained by modification of method 1.1.1.B. [19, 34]. The *in situ* formation of such salts can inhibit normal nucleophilic reactions [35, 36]. Quaternary ammonium chlorometallates have been synthesized from quaternary ammonium chlorides and transition metal chlorides, such as IrCl_3 and PtCl_4 , and are highly efficient catalysts for phase-transfer reactions and for metal complex promoted reactions [37].

1.1.3 Quaternary ammonium hydrogen difluorides and dihydrogen trifluorides

Quaternary ammonium hydrogen difluorides: KHF_2 (7.8 g, 0.1 mol) is added to the quaternary ammonium hydrogen sulphate (0.1 mol), neutralized with KHCO_3 (10 g), in CHCl_3 (500 ml) and H_2O (25 ml) and the mixture is stirred at room temperature for ca. 1 h. The organic phase is separated and evaporated to yield the quaternary ammonium hydrogen difluoride. Any dihydrogen trifluoride salt formed at the same time can be removed by dissolution of the product in MeCN and neutralization with anhydrous K_2CO_3 .

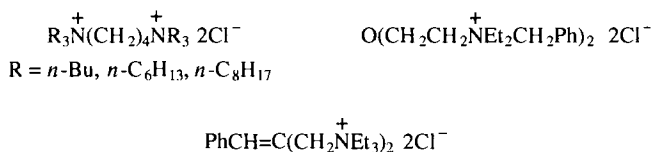
Quaternary ammonium dihydrogen trifluorides. Method A: The above procedure using a 50-fold excess of KHF_2 produces the ammonium dihydrogen trifluoride.

Method B: Aqueous HF (50%, 6 ml, 0.15 mol) and KHF_2 (11.7 g, 0.15 mol) in H_2O (35 ml) are added to TBA-F. $3\text{H}_2\text{O}$ (9.47 g, 30 mmol) in $\text{Cl}(\text{CH}_2)_2\text{Cl}$ (300 ml) and the mixture is stirred for 2 h at room temperature. The organic phase is separated and distilled azeotropically to remove H_2O and then evaporated under reduced pressure to yield TBA- H_2F_3 .

Quaternized azines and azoles have also been investigated as potential phase-transfer catalysts. 1-Alkyl-2- and 4-dialkylaminopyridinium salts [38, 39] have

catalytic activities comparable with Aliquat and are generally more stable thermally than is tetra-*n*-butylammonium bromide, except in the presence of base or sulphide ions when they converted rapidly into the corresponding 1-alkylpyridones and pyridithiones [40].

Several soluble 'multi-site' ammonium catalysts have been synthesized, examples of which are shown in Scheme 1.1 [e.g. 41–43]. Such catalysts have the advantage over single site catalysts in reactions involving divalent anions and, generally, in the lower amount of the salt required to obtain a catalytic effect.

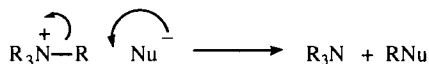


Scheme 1.1

The claim that *N*-acyl trialkylammonium salts are effective phase-transfer catalysts [44] has been discredited with evidence showing that the compounds were simple trialkylammonium salts, which were converted *in situ* into tetraalkylammonium salts in the course of the reactions [45].

Stability of quaternary ammonium salts

Quaternary ammonium salts are generally stable under neutral or acidic conditions up to 150°C, but decomposition can occur with the quaternary ammonium ion acting as an alkylating agent in its reaction with anions (Scheme 1.1). Soft nucleophiles, such as RS⁻, are more reactive with tetra-*n*-butylammonium bromide and benzyltriethylammonium chloride, although the latter salt also *C*-benzylates phenylacetonitrile under basic conditions [46]. These side reactions are considerably slower than the main catalysed reactions with, for example, a haloalkane and the amount of unwanted impurity in the final alkylated product is never greater than the amount of catalyst used (i.e. generally > 2%). Harder anions, e.g. R₂N⁻ and RO⁻, rarely react with the ammonium salts.



Scheme 1.2

In basic media, the ammonium salts are generally far more susceptible to degradation, but are more stable than the corresponding phosphonium salts [47]. This observation contrasts with their stabilities under neutral conditions, where the phosphonium salts are the more stable. In addition to reactions of the type shown in Scheme 1.2, the Hofmann degradation of symmetrical tetraalkylammonium salts is

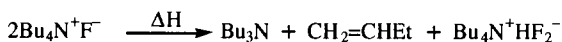
the major decomposition pathway leading to the tertiary amine and an alkene (Scheme 1.3).



Scheme 1.3

The order of stability is inversely proportional to the extractability of the ammonium hydroxide into the organic phase and therefore affects the salts of the more lipophilic cations to a greater extent. However, the extractability is also dependent on the counter anion and, as the concentration of hydroxide ion extracted by highly lipophilic ammonium iodides is minimal compared with the less lipophilic ammonium chlorides, the observed stabilities [47] of the salts, $\text{R}_4\text{NCl} \ll \text{R}_4\text{NBr} \ll \text{R}_4\text{NI}$, are not to be unexpected. The stabilities of the ammonium salts are decreased upon increasing the concentration of the base; changes in half-life times of *ca.* 25–50:1 have been noted upon changing from 50% to 15% aqueous sodium hydroxide [47]. The extractability of the hydroxide ion is inversely proportional to its concentration in the aqueous phase, but the lower degree of hydration of the extracted hydroxide ion and its concomitant greater basicity is considerably more important [48, 49].

Quaternary ammonium fluorides are hygroscopic and any attempt to remove the water results in decomposition of the salt. When tetra-*n*-butylammonium fluoride trihydrate is heated at 77°C under vacuum over phosphorus pentoxide an almost anhydrous form of the salt is obtained but, when further attempts are made to remove the remaining water, a Hofmann-type elimination occurs yielding but-1-ene and tetra-*n*-butylammonium hydrogen difluoride (Scheme 1.4) [e.g. 50]. Tetraethylammonium fluoride decomposes in a similar manner when heated and it is generally acknowledged that anhydrous ammonium fluorides do not exist and the many reports of their isolation probably relate to ‘almost anhydrous’ material or to the hydrogen difluoride salt.



Scheme 1.4

Chiral β -hydroxyethylammonium catalysts decompose under strongly basic conditions with the extrusion of a tertiary amine to produce chiral oxiranes, which contaminate the reaction products and lead to spurious conclusions about the enantioselective nature of the reaction (Chapter 12).

A large number of reviews of phase-transfer catalysis in general, incorporating the use of quaternary ammonium salts, have appeared since the 1960s [e.g. 18, 51–66]. Many of the early articles are of important historical interest, whereas the later reviews illustrate the manner in which applications of the technique have mush-

roomed over the past thirty years and provide a general overview of the scope of the reactions.

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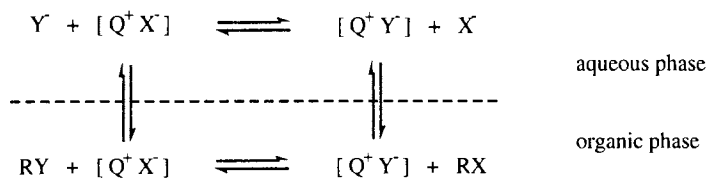
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1.2 MECHANISM OF PHASE-TRANSFER CATALYSIS

The following sections provide a simplified mechanistic overview of phase-transfer catalysis. For more detailed presentations, reference should be made to more modern comprehensive texts [e.g. 1–3].

Starks' extraction mechanism [4, 5]

In its simplest form, the phase-transfer catalysed nucleophilic substitution reaction, $RX + Y^- \rightarrow RY + X^-$, in which the active nucleophile Y^- is transferred from the aqueous into the organic phase, can be depicted by Scheme 1.5. The mechanism requires the 'extraction' of the nucleophilic anion by the quaternary ammonium cation Q^+ as the ion-pair $[Q^+Y^-]$ into the organic phase, where the nucleophilic reaction can take place. Subsequent to the reaction the 'spent' catalyst forms an ion pair with the released anion X^- and equilibration of $[Q^+X^-]$ between the two phases establishes a

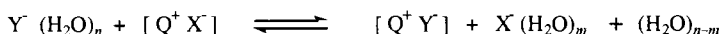


Scheme 1.5

cycle, which will continue until all the nucleophilic species Y^- or the organic substrate RX is consumed.

Kinetic evidence [6] for the nucleophilic reaction taking place entirely in the bulk of the organic phase is provided by the observation that the rate of the reaction rapidly reaches a maximum with a stirring rate of *ca.* 250–300 rpm and is virtually invariant above this rate. As the equilibration of the associated ion-pairs in the aqueous phase and their partition across the phase boundary can be assumed to be faster than the nucleophilic substitution reaction then, with an excess of the nucleophilic anion in the aqueous phase and a fixed concentration of catalyst, the concentration of the nucleophile Y^- in the organic phase is effectively constant and the observed rate of consumption of organic substrate is pseudo-first order [e.g. 5, 7], as required for the nucleophilic reaction to be totally homogeneous in the organic phase. The reaction rate is directly proportional to the concentration of the catalyst, which eliminates the possibility of the quaternary ammonium salts acting as cationic surfactants for which a non-linear correlation between the reaction rate and the concentration of the quaternary ammonium catalyst would exist, as a result of changes in the stable micelle size with changes in the concentration of the surfactant [6].

The thermodynamics of the 'extraction' mechanism is extremely complex. In the initial equilibration of the ion pairs (Scheme 1.6) account has to be taken not only of the relative stabilities of the ion-pairs but also of the relative hydration of the anionic species. Assuming the complete non-solvation of the ion-pairs, the formation of the ion-pair $[\text{Q}^+ \text{Y}^-]$ will generally be favoured when the relative hydration of X^- is greater than that of Y^- . However, in many cases, the anion of the ion-pair is hydrated [8–11] (Table 1.1) and this has a significant effect both on equilibrium between the ion-pairs in the aqueous phase and the relative values of the partition coefficients of the two ion-pairs $[\text{Q}^+ \text{X}^-]$ and $[\text{Q}^+ \text{Y}^-]$ between the two phases.



Scheme 1.6

Generally, where the anion is poorly solvated in the aqueous phase, there is a greater propensity for the ion-pair to reside in the organic phase and, consequently, the overall effect of the quaternary ammonium catalyst is influenced by the initial choice of counter anion of the catalyst or by the anion that is generated in the

TABLE 1.1

Hydration of inorganic anions in chlorobenzene in liquid:liquid two-phase systems

Anion	Hydration of anion in chlorobenzene	
	With aqueous medium	With 50% aqueous NaOH
F ⁻	8.5	3.5
RCO ₂ ⁻	4.0	1.4
Cl ⁻	3.4	0.4
N ₃ ⁻	3.0	0.3
Br ⁻	2.0	0.4
I ⁻	1.1	0.2

nucleophilic substitution reaction. The relative values of the partition coefficients of $[Q^+X^-]$ and $[Q^+Y^-]$ determine the kinetic behaviour of the reactive system. Detailed kinetic studies of the poisoning effects of 'foreign' anions released during the course of nucleophilic substitution reactions have been undertaken [12–14]. Where $k_{[Q^+X]}:k_{[Q^+Y]} > 1$, catalyst poisoning occurs and the catalyst becomes ineffective whereas, when $k_{[Q^+X]}:k_{[Q^+Y]} = 1$, the nucleophilic reaction follows second order kinetics and, when $k_{[Q^+X]}:k_{[Q^+Y]} < 1$, pseudo-first order kinetics are observed. Thus, for example, quaternary ammonium iodides are poor catalysts for liquid:liquid phase-transfer catalytic reactions, as not only does their low hydration lead to poor equilibration with more hydrated anions, but their concomitant high partition coefficient also mitigates against the transfer of other anions into the organic phase. Similarly, alkylation reactions utilizing iodoalkanes fail unless a stoichiometric amount of the catalyst is used, as the released iodide ion produced during the course of the reaction remains in the organic phase and competes for formation of the ion-pair with, for example, the carbanion [15, 16]. Conversely, quaternary ammonium hydrogen sulphates are frequently a good choice of catalyst as their partition coefficients are low compared with other ammonium salts.

In general, the degree of hydration of the transferred anions in the organic phase is considerably lower than in the aqueous phase. Hydration of the ion-pair is relatively insensitive to the nature of the ammonium cation and it has been proposed that the water is only weakly bonded, so the activation energy for the de-solvation of the anion is lower than in a bulk aqueous phase [8]. Hydration can be reduced or virtually eliminated under liquid:liquid two-phase conditions using a 'dehydrating' 50% aqueous solution of sodium hydroxide (or 60% aqueous potassium hydroxide) in place of water [e.g. 9–11, 17–19] (Table 1.1). Under these conditions, the hydroxide anion is preferentially hydrated and is not transferred into the organic phase. Among other factors, the nucleophilicity of the anion in the organic phase is related to its degree of hydration and the use of 50% aqueous sodium hydroxide produces two- to tenfold increases in nucleophilic substitution reaction rates [e.g. 7, 9, 11, 20–22] compared with transfer of the partially hydrated anion from a non-basic medium. The combination of the quaternary ammonium catalyst and hydroxide is a more effective dehydration system for most anions than is a crown ether:hydroxide

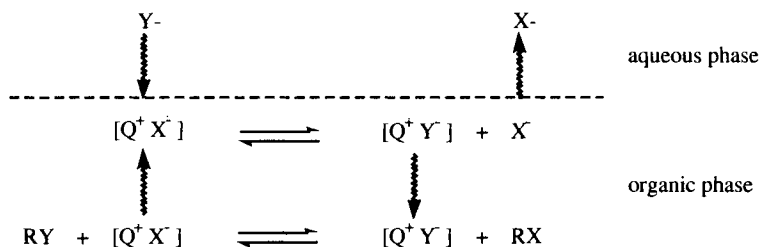
system [21]. Where the reactive substrate is susceptible to hydrolysis by concentrated aqueous sodium hydroxide, the dehydrating effect can be maintained at a lower concentration of base by the addition of potassium fluoride without prejudicing the basic character of the aqueous phase [23].

The extraction mechanism accommodates a large number of anionic reactions and provides a rationale for general absence of catalytic activity by hydrophilic ammonium salts, e.g. tetramethylammonium halides [24, 25], which have negligible solubility in organic solvents. Similarly, owing to the highly hydrophilic nature of the hydroxide anion, the mechanism is also untenable as a rationalization for the majority of base-catalysed reactions.

Lower molecular-weight quaternary ammonium halides, which partition across the two-phase system, transfer anions in measurable concentrations from the aqueous to the organic phase but, in contrast, many of the higher-molecular-weight quaternary ammonium halides with more than *ca.* 30 carbon atoms are virtually insoluble in aqueous media and their partition coefficients between aqueous and organic phases preclude the transfer of anions efficiently across the interface by the extraction process and yet catalysts, such as Aliquat® 336 and Adogen® 464, are extremely effective catalysts.

Makosza's interfacial mechanism [26]

Kinetic studies using liquid membranes of the catalytic efficiency of ammonium salts [27] indicate that concomitant transfer of the organic cation with the anion is not a prerequisite for effective catalysis and leads to an alternative rationalization of the effectiveness of the lipophilic catalyst in terms of an anion exchange reaction at the interface between the two phases, followed by the diffusion away from the interface of the ion-pair and its subsequent reaction with organic substrate in the bulk of the organic phase [28] (Scheme 1.7). The interfacial mechanism is more specific to the highly lipophilic catalysts [25] and, as with all interfacial reactions, the rate of transfer of the anion from the aqueous phase depends strongly on the efficient mixing (i.e. stirring rate) of the two phases [e.g. 29]. Additionally, as with the extraction mechanism, the overall efficiency of the interfacial mechanism depends on hydration of the anions X^- and Y^- , the relative stabilities of the ion-pairs $[Q^+X^-]$ and $[Q^+Y^-]$, and their relative solubility in the organic phase.



Scheme 1.7

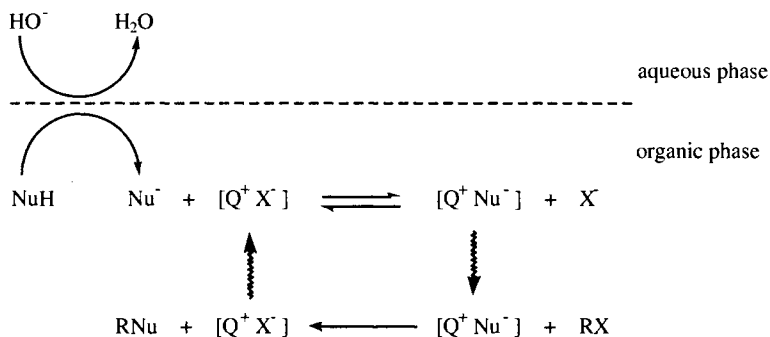
The interfacial mechanism probably competes to some extent with the extraction mechanism, particularly with the less lipophilic catalysts. The dependence of the rate of many nucleophilic substitution reactions on the stirring rate up to 250–300 rpm and the independence of the reaction rate at higher stirring rates has been taken as evidence for a change over from a predominant interfacial mechanism to an extraction process. The interfacial mechanism is also particularly relevant to base-initiated reactions.

Base-initiated reactions [30]

Catalytic transfer of hydrated hydroxide anions into an organic phase is extremely poor [31, 32]. The transfer decreases as the concentration of the base is increased [19], in spite of the lower degree of hydration of the ion. Not unexpectedly, the proton affinity of the transferred hydroxide anion in the organic phase increases, as it also does at the interface. Despite their low partition coefficients, which are difficult to measure accurately, there are kinetic data which appear to support an extraction mechanism using highly lipophilic catalysts for several base-initiated reactions, such as isomerization reactions, ester hydrolysis, the conversion of benzyl chloride into benzyl alcohol, and dehydrohalogenation of haloalkanes [33–38]. In particular, the observed Hoffman degradation of the catalyst [39] during the catalysed conversion of 4-chlorobutyronitrile into cyanocyclopropane under basic solid:liquid two-phase conditions and the kinetic data have been taken as unequivocal proof of the extraction of the hydroxide anion into the organic phase [40]. The order of extractability of anions by quaternary ammonium cations is $I > Br > Cl > HO > SO_4^{2-}$. Thus, tetra-*n*-butylammonium hydrogen sulphate is a better catalyst for transfer of hydroxide anions into an organic phase than are the halides [e.g. 31–36, 41] and the iodides are very much poorer in their ability to transfer hydroxide ions into the organic phase than are chlorides [42]. However, in the dehydrohalogenation reaction, an equimolar amount of the catalysts is required in order to counteract the effect of poisoning by the released halide ion [33, 34].

The addition of an alcohol to the basic two-phase system increases the apparent extraction of base into the organic phase, but it is generally acknowledged that it is the alkoxide anion which is being transferred [e.g. 43–50]. Optimum conditions for this co-catalytic effect requires the formation of highly lipophilic and highly basic alkoxide anions, either in the aqueous phase or at the interface.

The interfacial mechanism provides an acceptable explanation for the effect of the more lipophilic quaternary ammonium salts, such as tetra-*n*-butylammonium salts, Aliquat® 336 and Adogen® 464, on the majority of base-initiated nucleophilic substitution reactions which require the initial deprotonation of the substrate. Subsequent to the interfacial deprotonation of the methylene system, for example the soft quaternary ammonium cation preferentially forms a stable ion-pair with the soft carbanion, rather than with the hard hydroxide anion (Scheme 1.8). Strong evidence for the competing interface mechanism comes from the observation that, even in the absence of a catalyst, phenylacetonitrile is alkylated under two-phase conditions using concentrated sodium hydroxide [51].



Scheme 1.8

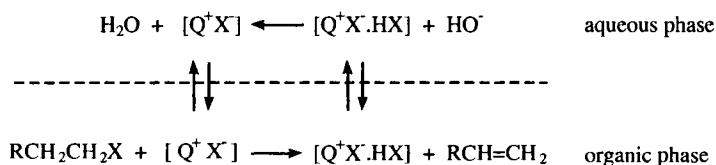
Although less lipophilic, the catalytic effect of the lower molecular-weight quaternary ammonium salts, such as tetraethylammonium and benzyltriethylammonium chloride, in base-initiated reactions is rationalized in terms of the greater availability of the positive charge to form an ion-pair with the anion derived from the substrate [52]; tetramethylammonium salts are too hydrophilic to be soluble in the organic medium. Benzyltriethylammonium chloride is frequently the catalyst of choice for the base-catalysed formation of dihalocarbenes and for the alkylation of activated methylene compounds; kinetic data strongly support the interfacial mechanism for all such reactions [e.g. 29, 53–55]. Similarly, the stereochemistry of the products from the Darzens reaction and in the base-catalysed formation of cyclopropanes, with and without the presence of quaternary ammonium salts (see Chapter 12.1) is strongly supportive of an interfacial deprotonation mechanism rather than extraction of the base into the organic phase.

It has been demonstrated that the relative accessibility of the quaternary ammonium cation to the anion controls the *C*- vs *O*-alkylation of methylene ketones [52, 56]. With smaller ammonium cations, the yield of *C*-alkylated product is high, as the strong association between the 'hard' oxygen centre of the substrate anion and the more accessible 'harder' ammonium cation hinders nucleophilic attack at the oxygen atom. Conversely, with bulkier 'softer' ammonium ions, the weaker association with the oxygen centre leads to a greater yield of *O*-alkylated product. The overall decrease in reactivity of the system as the lipophilicity of the cation increases mitigates against Starks' extraction mechanism. The ratio of *O*- to *C*-alkylated products is also controlled by the amount of water transferred into the organic phase. With 50% aqueous sodium hydroxide, with which virtually no water is transferred, the ratio is 1.37 : 1 whereas, with more dilute base (20%) and a greater transfer of water to the organic phase, the ratio is 1.1 : 1 [57]; under 'anhydrous' solid:liquid conditions (see later) the *O*:*C* ratio is 1.46 : 1. These observations are interpreted in terms of solvent-separated ion pairs in which the water is H-bonded to the oxygen atom thereby protecting it from alkylation.

Reverse transfer mechanism

As an alternative to the extraction and interfacial mechanisms, hydroxide promoted dehydrohalogenation reactions may also occur, not by proton removal from the

substrate at the interface or in the bulk of the organic phase, but by a reverse transfer mechanism whereby the halogen acid released in the bulk of the organic phase is transferred as a complex ion-pair into aqueous phase, where it is neutralized (Scheme 1.9). Such a mechanism has been proposed for basic liquid:liquid conditions catalysed by relatively weakly lipophilic ammonium salts [47, 52]. Kinetic studies [58] indicate that the rate of elimination varies little with the concentration of aqueous base and that it is not the rate-determining step. The process is diffusion controlled and the rate is proportional to the stirring rate supporting the proposed interfacial neutralization [59]. The mechanism might also be prevalent for other reactions in which the hydroxide extraction process is negligible.



Scheme 1.9

The ability of quaternary ammonium halides to form weakly H-bonded complex ion-pairs with acids is well established, as illustrated by the stability of quaternary ammonium hydrogen difluoride and dihydrogen trifluorides [e.g. 60] and the extractability of halogen acids [61]. It has also been shown that weaker acids, such as hypochlorous acid, carboxylic acids, phenols, alcohols and hydrogen peroxide [61–64] also form complex ion-pairs. Such ion-pairs can often be beneficial in phase-transfer reactions, but the lipophilic nature of H-bonded complex ion-pairs with oxy acids, e.g. $[\text{Q}^+\text{X}^-\text{HOAr}]$ or $[\text{Q}^+\text{X}^-\text{HO.CO.R}]$, inhibits O-alkylation reactions necessitating the maintenance of the aqueous phase at $\text{pH} > 7.0$ with sodium or potassium carbonate to ensure effective formation of ethers or esterification [49, 64].

Solid:liquid two-phase reactions [65]

The problems encountered in the catalytic transfer of highly hydrophilic anions from aqueous solutions into the organic phase can be countered by the use of ‘anhydrous’ solid salts; the organic reactant is dissolved in the organic solvent or, if liquid, may be used neat. Solid:liquid two-phase reactions using ammonium salts have widespread application (see, for example, the many examples cited in later chapters) frequently with shortened reaction times, lower reaction temperatures, and higher yields [e.g. 66, 67] and are generally superior to solid:liquid reactions catalysed by crown ethers [68]. The process is particularly useful in base-initiated reactions with fluorides, hydroxides or carbonates.

It was originally proposed that ion exchange occurred at the solid surface of the salts, but it has been demonstrated that reaction is extremely slow with totally anhydrous salts [69] and that a trace of water is essential for success of the reactions [e.g.

68–75]. It is probable that high lattice energies mitigate against ion exchange on the ‘anhydrous’ salts and that a saturated layer on the surface of the solids assists the exchange process. Water will be transferred from the ‘moist’ solid into the organic phase by the ion-pairs and use of an excessive amount of catalyst has been shown to inhibit the catalytic process by removal of the water layer from the solid salt [69, 76].

Hydroxide initiated reactions are more effective under solid:liquid conditions than they are under liquid:liquid conditions, even when 50% aqueous sodium hydroxide is used [77]. Although the interfacial formation of substrate anion by direct reaction with the base at the ‘solid’ surface remains an important mechanism, the probability of ion-pair formation and transfer of the hydroxide anion into the bulk of the organic phase is higher than for liquid:liquid systems [e.g. 66], as shown by the hydrolytic side reactions that occur, e.g. ester hydrolysis during *C*-alkylation of malonic esters [67]. The lower propensity of carbonate ions to form lipophilic ion-pairs [e.g. 32], even in highly polar solvents [78], leads to the conclusion that such base-catalysed reactions are initiated by an interfacial generation of the organic substrate anion [67, 79].

In contrast with standard liquid:liquid two-phase alkylation reactions, it is possible to use iodoalkanes with only catalytic amounts of the ammonium salts in the absence of an added solvent under solid:liquid conditions [e.g. 80].

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1.3 CHOICE OF CATALYST

With so many commercial quaternary ammonium salts available, the choice of the most appropriate phase-transfer catalyst is confusing and yet very important for optimization of reaction conditions.

The effectiveness of the catalyst can be considered from two aspects: (a) the ability of the quaternary ammonium cation to transfer the reactive nucleophilic anion across the two-phase interface, and (b) the enhanced reactivity of the anion in the organic phase.

In many reactions, transfer of the anion across the interface and subsequent diffusion into the bulk of the organic phase will not be the rate-determining step when lipophilic catalysts are used, but the effect of less lipophilic catalysts may be influenced more by the anion and the mechanism of the transfer process. Thus, for example, the reactive anion is frequently produced in base-initiated reactions by proton extraction from the substrate at the two-phase interface and diffusion of the ion-pair contributes to the overall kinetics of the reaction. Additionally, the reactivity of the anion depends on its degree of hydration and on its association with the quaternary ammonium cation. In most situations, the activity of the transferred anion is enhanced, compared with its reactivity in aqueous media, as its degree of hydration is reduced, whereas a relatively weak electrostatic interaction between the two ions resulting from the bulkiness of the cation enhances the reactivity of the anion by making it more available for reaction and will be a major factor in the rate-determining step.

Generally, the more lipophilic the quaternary ammonium cation, the greater is its effectiveness in transferring nucleophilic anions into the organic phase. However, ammonium cations having short linear alkyl chains form stronger ion-pairs than those having longer linear or more bulky alkyl chains. Ideally, at least one alkyl chain should be relatively short to provide the optimum balance between lipophilicity and a strong ion-pair association. The influence of the structure of the ammonium cation upon its catalytic effect has been quantified as a q-factor [1], which is

equivalent to the sum of the reciprocals of the number of carbon atoms in each alkyl group of the cation. Generally, a value of $q > 1.0$ indicates a relatively high lipophilicity with a favourable transfer of the ion-pair into the organic phase, but a value of $q < 1.0$ indicates a high reactivity of the anion in the organic phase, as its association with the cation is relatively weak.

The tetraethylammonium cation ($q = 2$) forms stronger ion-pairs than does the tetra-*n*-butylammonium cation ($q = 1$), but the resultant ion-pairs have lower lipophilicity and, consequently, are poorer phase-transfer catalysts. It is self-evident that with increasing chain length, the catalytic effect of symmetrical tetraalkylammonium salts should increase initially, but then fall away as the ion-pair association constant decreases. Similarly, although benzyltriethylammonium chloride is a frequently used catalyst, it has a relatively low lipophilicity and benzyltributylammonium chloride is a better catalyst. The exceptional catalytic effect of Adogen® 464 and Aliquat® 336 (methyltrioctylammonium chloride, $q = 1.38$) combines a high overall lipophilicity and a relatively strong ion-pair association with most anions. The hydrogen sulphate anion and divalent anions are only transferred into the organic phase with any catalytic effect by quaternary ammonium cations having q values > 1 , e.g. di(dodecyl)dimethylammonium halides ($q = 2.17$) [2]. Thus, with some knowledge of the mechanism of the process and the rate-determining step, it is possible to make an informed guess of the most appropriate catalyst to use.

Factors related to the mechanism of the catalytic effect also influence the choice of catalyst. For example, the use of the weakly lipophilic benzyltriethylammonium chloride in aqueous sodium hydroxide would not be an ideal combination if the objective was to transfer the hydroxide ion into the organic phase, but it is the catalyst of choice in Makosza's procedure for the generation of dichlorocarbene, where transfer of the hydroxide is not critical and, in fact, where its transfer with associated water would be detrimental to the stability of the carbene in the organic phase. Conversely, the use of highly lipophilic tetra-*n*-butylammonium iodide is a poor choice of catalyst for the transfer of other nucleophilic anions under liquid:liquid two-phase conditions owing to its high partition coefficient, but its use under solid:liquid conditions in the absence of an added solvent is acceptable. Long-chain ammonium salts of the general formula $(C_nH_{2n+1})NMe_3^+X^-$ promote nucleophilic reactions in two-phase systems by the formation of micelles rather than by a phase-transfer mechanism [e.g. 3, 4].

Other factors important to the choice of catalyst are its stability under the reaction conditions (see Section 1.1) and its removal from the organic phase at the end of the reaction. Ideally, the catalyst should be sufficiently hydrophilic to be washed from the product by water, but any catalyst having this property has, by implication, a lower lipophilicity and lower catalytic effect. Where the product is volatile, it can be separated from the catalyst and isolated by fractional distillation of the organic phase or, alternatively, the catalyst can be precipitated from the concentrated organic phase by the addition of a non-polar solvent, such as diethyl ether, and removed by filtration. On a small scale, the catalyst can be separated efficiently by direct chromatography of the organic phase from, for example, silica. This procedure is, however,

laborious and costly on a large scale, even where the solvents and adsorbent can be recovered. Polymer-bound catalysts have the advantage over soluble catalysts of ease of removal, but are generally more expensive. In principle, they can be recycled, but they are as susceptible as the soluble catalysts to chemical decomposition, and have an additional susceptibility to physical disintegration.

More detailed discussions of the optimum choice of quaternary ammonium salt for phase-transfer catalysis are available elsewhere [1, 5–8].

In the following chapters, published procedures are given for a wide range of phase-transfer catalysed reactions. Particular catalysts, reaction conditions, and work-up procedures are recommended. In general, these are thought to be the optimum conditions but, where there are viable alternatives, they are indicated.

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1.4 SUPPORTED CATALYSTS

The removal of highly lipophilic catalysts from the reaction product poses problems, which can be obviated by binding the ammonium catalyst to a solid support. As well as being easily removed by filtration and recycled, such catalysts also have potential application in continuous flow phase-transfer catalytic processes.

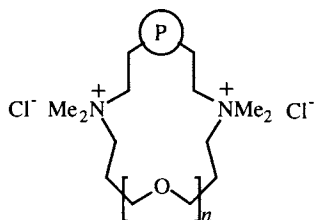
Liquid:liquid:solid polymer-bound catalytic systems – ‘triphasic catalysis’ [1] – have been successfully employed for halogen exchange [e.g. 1–4], synthesis of azides, nitriles, ethers and esters [e.g. 1–8], alkylation of activated methylene groups [4, 9, 10], generation of dichlorocarbene [e.g. 1–3], elimination [2], oxidation reactions [2, 3] and the ring-opening of oxiranes by thiols and thiocarboxylic esters [11]; chiral polymer-bound catalysts induce enantiomeric control of, for example, the Darzens reaction [12, 13] and the addition of methanol to ketenes [14, 15]. Commercial anion exchange resins, e.g. Amberlyst A-26, can be used, but they have reduced catalytic activity [16] necessitating vigorous reaction conditions; specially prepared catalysts with spacer groups between the polystyrene backbone and the cationic centres are more effective having activities as high as that of the free soluble ammonium salts [e.g. 4, 6, 7, 17, 18]. Although the mechanism of triphasic catalysis

is not fully understood, kinetic studies [19] have shown that the rates of nucleophilic reactions are proportional to the number of cationic centres on the resin, but that optimum rates are obtained with only 10% substitution of the polystyrene chain and that dramatic decreases in reaction rates are observed with higher degrees of substitution.

Triphase catalysis has been used with solid inorganic reagents in non-polar solvents or with the neat organic substrate [e.g. 20] in the preparation of ethers, esters, nitriles and nitroalkanes, and in halogen exchange, oxidation reactions and alkylation of activated methyl groups. As with solid:liquid systems using non-bound catalysts, a trace of water is required for optimum reaction conditions and, because of the nature of the system, mechanical stirring causes disintegration of the polymer and ultrasonic agitation is recommended. Reviews of the basic principles of triphase catalysis are available [e.g. 21].

In an extension to triphase catalysis, two-phase systems are used employing stoichiometric amounts of the preformed polymer-bound catalyst bearing the reactive anion. Again the ready removal of the catalysts is advantageous and the procedure has been utilized with success for example for halogen exchange reactions [e.g. 22–24], the synthesis of azides, nitriles, nitro alkanes, phenyl ethers, esters and ureas [e.g. 24–29], C-alkylation of activated methylene groups [29], oxidation reactions with preformed ammonium chromate [30, 31], reductions with preformed ammonium borohydride [32], α -halogenation of alkyl ketones and addition reactions with alkynes and alkenes [e.g. 33–35] using preformed polymer-bound ammonium tribromide and dichloroiodate salts. When equimolar amounts of the dichloroiodate resin and alkene is used, a mixture of the dichloro- and chloroiodoalkane is produced whereas, with an excess of the resin, only the dichloroalkanes are isolated [35]. Preformed polymer-bound ammonium carbonate converts haloalkanes into the corresponding alcohols [36].

Polymer-bound catalysts containing both quaternary ammonium centres and oligo-(oxyethylene) links of the type shown in Scheme 1.10 have been synthesized [34]. There is an increase in catalytic activity resulting from a cooperative effect of the two types of catalyst upon nucleophilic reactions, compared to that of simple quaternary ammonium catalysts and crown ethers.



Scheme 1.10

Ammonium salts immobilized on silica or alumina differ in their properties in several respects, compared with polymer-bound catalysts. Unlike the polymer-bound catalysts, which require pre-swelling of the resin [e.g. 4, 38] with the organic phase to allow ready access of the substrate to the active catalytic site, silica-immobilized catalysts have no induction period and the reactions can be conducted in non-polar solvents without stirring [39]. The polar character of the support aids anion exchange at the cationic centres in the nucleophilic reactions and, as with the polymer-bound systems, reactions follow pseudo first-order kinetics with the reaction rates being proportional to the concentration of the cationic centres bound to the silica. A range of reactions, including halogen exchange, hydride reductions, synthesis of amines and esters, etc., have been conducted successfully [e.g. 39, 40] and it is reported that quaternary ammonium fluorides can be immobilized on silica in an anhydrous form and that the catalysts are highly effective for Michael addition reactions and *C*-alkylation of activated methylene groups [41].

A general review of synthesis and reactivity of silica-immobilized 'onium catalysts, which deals mainly with phosphonium salts, is available [42].

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- 2 -

Simple Nucleophilic Exchange Reactions and Aromatic Substitution Reactions

2.1 SIMPLE ALIPHATIC S_N REACTIONS

The formation of C–O, C–S, C–N and C–C bonds by nucleophilic substitution is described in subsequent chapters. In this section the synthesis of haloalkanes by halogen–halogen exchange and related reactions are presented.

Liquid:liquid conditions are not usually successful for the conversion of chloroalkanes into the corresponding bromo derivatives, as the reaction is reversible and, consequently, requires high concentrations of the inorganic bromide salt [1]. Kinetic data indicate that the conversion of bromoalkanes into the corresponding chloro compounds is *ca.* 150 times faster than the reverse process [2]. Solid:liquid conditions are more successful [3]. It has also been established that the position of equilibrium in the exchange process depends on the inorganic cation [e.g. 4–8], for example, lithium or calcium bromide is superior to sodium or potassium bromide. In an alternative procedure, the chloroalkane is treated with a volatile brominating agent and either the bromoalkane or the volatile chloride by-product is removed continuously during the reaction. It is noteworthy that the conversion of chloroalkanes into iodoalkanes has been accomplished under liquid:liquid conditions [9–11], whereas the reverse reaction occurs when iodoalkanes are heated with tetra-*n*-butylammonium chloride with the chloroalkane distilling as it is formed [9].

Hydrogen bromide, trimethylsilyl bromide and acetyl bromide have all been proven to be suitable bromide transfer agents [e.g. 12, 13]. Tetra-*n*-butylammonium salts catalyse the interconversion of dichloroalkanes into bromochloroalkanes and chloriodoalkanes upon reaction with an excess of bromo- and iodobutane, respectively [14]. Similarly, mixed bromochloromethanes are obtained from the reaction of dibromochloromethane with benzyltriethylammonium chloride under basic conditions [15].

A high-yielding direct conversion of alcohols into the corresponding bromo derivatives has been reported using anhydrous hydrogen bromide in the presence of Aliquat [16]. Secondary alcohols lead to isomeric mixtures, presumably via an elimination–addition process. A patented process describes the analogous

conversion of alcohols into chloro compounds [17]. Nucleophilic displacement of alkanesulphonate groups using potassium halides without the addition of an organic solvent is successful for chlorides, bromides and iodides [e.g. 18, 19] but, generally, more vigorous conditions are needed for the formation of the fluorides [20, 21]. Moderate yields (50–80%) of halo compounds have been achieved by the prolonged reaction of tosylates with an excess of the tetra-*n*-butylammonium halides [22] and catalysed halogen exchange between chloroform and bromoform under basic conditions produces dibromochloromethane (72%) and bromodichloromethane (48%) [23].

2.1.1 Conversion of chloroalkanes into bromoalkanes

Method A: The chloroalkane (0.1 mol) and CaBr_2 (10.53 g) are stirred with THA-Br (0.87 g, 2 mmol) at 110°C for 24 h. CH_2Cl_2 (25 ml) is added and the organic phase is separated, washed with H_2O (2×25 ml), dried (Na_2SO_4), and fractionally distilled to yield the bromoalkane [e.g. C4–C8 bromides, 89–92%; PhCH_2Br , 94%; CH_2Br_2 , 62% with 30% ClCH_2Br ; $(\text{CH}_3\text{Br})_2$, 53% with 38% $\text{Cl}(\text{CH}_3)_2\text{Br}$]. Similar yields are obtained using LiBr (8.6 g) and Aliquat (2 g, 5 mmol) at 98°C for ca. 20 h in the absence of a solvent.

Method B. Conversion of chloroalkyl carbonates into bromoalkyl carbonates using HBr: HBr (8.1 g, 0.1 mol) is bubbled steadily into the chloroalkyl carbonate, $\text{RCH}(\text{Cl})\text{OCO}_2\text{R}'$, (0.1 mol) containing TBA-Br or TBBA-Cl (1.4 mmol) at 85 – 90°C over ca. 6 h. The apparatus is fitted with a condenser cooled to -83°C with dry ice/EtOAc to prevent distillation of the HBr, but allowing free passage of HCl. CH_2Cl_2 is added to the cooled reaction mixture and the organic solution is washed well with H_2O , dried (MgSO_4), and fractionally distilled to yield the bromoalkyl carbonate [e.g. $\text{R} = \text{Me}$, $\text{R}' = \text{Et}$, 82%; *n*-Bu, Me, 49%].

Method C. Conversion of chloroalkyl carbonates into bromoalkyl carbonates using Me_3SiBr or AcBr : AcBr or Me_3SiBr (0.12 mol) is added to the chloroalkyl carbonate, $\text{RCH}(\text{Cl})\text{OCO}_2\text{R}'$, (0.1 mol) containing TBA-Br or Aliquat (1.4 mmol) and the mixture is heated at 85 – 90°C over ca. 24 h such that the bromoalkyl carbonate fractionally distils continuously [e.g. $\text{R} = \text{Me}$, $\text{R}' = \text{Ph}$ 91%; Me, Et 82%].

2.1.2 Conversion of chloroalkanes into iodoalkanes

The chloroalkane (0.1 mol) in PhCl (100 ml) is heated with NaI (16.5 g, 0.11 mol) and TBA-I (5.17 g, 14 mmol) in H_2O (50 ml) for 90 min. The mixture is cooled to 0°C and the iodoalkane is isolated in a manner analogous to that described in 2.1.1.A.

2.1.3 Conversion of dichloroalkanes into iodo- or bromochloroalkanes

n-BuBr or *n*-BuI (2 mol), $\text{Cl}(\text{CH}_2)_n\text{Cl}$ (1.5 mol) and TBA-Br or TBA-I (70 mmol) are heated in an apparatus fitted with a fractionating column. The mixture is heated for 5 h during which time a low-boiling-point fraction distils. The residual mixture is washed with H_2O (2×250 ml) and filtered through silica. The filtrate is fractionally distilled to yield the chloriodo- or bromochloroalkane (>90%) with 98% purity.

2.1.4 Dibromochloromethane and bromodichloromethane

Aqueous NaOH (50%, 200 ml) is added dropwise to CHCl₃ (240 g, 2 mol), CHBr₃ (506 g, 2 mol) and TEBA-Cl (3 g, 13 mmol). After the initial addition of NaOH (10 ml), the exothermic reaction is cooled to 35 °C and the remaining NaOH is added over 10 min. The mixture is stirred at 35 °C for 1 h and then poured into H₂O (450 ml). The organic phase is separated, washed well with HCl (1 M) and H₂O, dried (MgSO₄), and fractionally distilled to give CHBrCl₂ (108 g) and CHBr₂Cl (225 g) with CHCl₃ (106 g) and CHBr₃ (101 g).

2.1.5 Synthesis of chloro-, bromo- and iodoalkanes from sulphonates

The alkyl methanesulphonate (50 mmol), the appropriate potassium halide (50 mmol) and Aliquat (11.27 g, 2.5 mmol) in H₂O (5 ml) are stirred at *ca.* 100 °C. The aqueous phase is separated and extracted with *n*-C₈H₁₂ (50 ml). The combined organic solutions are washed sequentially with H₂O, conc. H₂SO₄, and H₂O, dried (CaCl₂), and fractionally distilled to yield the haloalkane [e.g. *n*-C₈H₁₇Cl (74%) from *n*-C₈H₁₇OSO₂Me after 90 min; *n*-C₈H₁₇Br (73%) after 30 min; *n*-C₈H₁₇I (70%) after 20 min].

The use of 'anhydrous' quaternary ammonium fluoride has been advocated for the synthesis of fluoroalkanes [e.g. 24, 25], but it has been demonstrated that water is critical (generally recommended as 0.33 mol equivalent) for optimum yields in the solid:liquid phase conversion of chlorides into fluorides using inorganic fluorides or tetra-*n*-butylammonium fluoride [26–29]. It has also been suggested that, if a solvent is to be used, formamide leads to high yields of the fluoro compounds [28]. Glycosyl fluorides have been obtained from glycosyl tosylates using tetra-*n*-butylammonium fluoride in acetonitrile [24, 30].

An excess of tetra-*n*-butylammonium fluoride is used for the conversion of 1,1-dichlorocyclopropane into the corresponding difluoro derivatives (40–46%), which are not readily obtained by difluorocarbene insertion into alkenes (see Chapter 7) [31]. Similarly, chlorodiazirines are converted into fluorodiazirines [32]. Tetra-*n*-butylammonium hydrogen difluoride has been described as a versatile and efficient reagent for the nucleophilic displacement of a range of functional groups by the fluoride anion with yields >90% being readily attainable [33]. Tetra-*n*-butylammonium dihydrogen trifluoride reacts with alkynes to yield fluoroalkenes [34]. Reaction with the hydrogen difluoride salt is less effective.

The conventional conversion of carbonyl systems by sulphur tetrafluoride into difluoroalkyl compounds has been modified in the reaction of dithioacetals with tetra-*n*-butylammonium dihydrogentrifluoride and *N*-bromo- or *N*-iodosuccinimide. Yields of the difluoroalkanes are generally in excess of 70% [35].

Tetra-*n*-butylammonium triphenyldifluorosilicate has been found to be a more reliable source of fluoride ions compared with the simple fluoride or hydrogen fluoride salts. The salt is available as an anhydrous non-hygroscopic material [36] and, although it is less nucleophilic and a weaker base than the ammonium fluo-

ride, it can be used for the displacement of halide or tosyloxy groups by fluoride. Generally, more vigorous reaction conditions are required (e.g. 24 h under reflux in aceto-nitrile), but yields are higher than observed for the corresponding reaction with the ammonium fluoride with a significantly lower production of elimination products [36]. Tetra-*n*-butylammonium difluorotriphenylstannate has also been used as an alternative to the fluoride salt for the conversion of bromoalkanes into fluoroalkanes and for the synthesis of α -fluoroketones from silyl enol ethers [37].

Fluoroalkanes have been prepared by the catalytic reaction of fluoride ion with diazoalkanes, but little synthetic use has been made of the process [38].

2.1.6 Synthesis of fluoroalkanes

Method A: The chloro or bromoalkane (3.3 mmol) is added to 'anhydrous' TBA-F (2.6 g, 10 mmol) and the mixture is stirred until the reaction is complete (see Table 2.1). For the highly volatile fluoroalkanes, isolation is accomplished by warming the mixture to *ca.* 45°C and 'blowing off' the product with dry N₂ into a cooled gas trap. Less volatile fluoroalkanes are isolated by the addition of H₂O (50 ml). The mixture is extracted with *n*-C₅H₁₂ (10 ml + 4 × 5 ml). The organic extracts are washed well with saturated aqueous CaCl₂. Excess TBA-F is removed by titration with bromine, followed by washing with aqueous Na₂S₂O₃ (1M), and the dried (MgSO₄) organic solution is evaporated to yield the fluoroalkane.

Method B: The alkyl tosylate (30 mmol) is added to 'anhydrous' TBA-F (15.7 g, 60 mmol) either in the absence of a solvent, or in MeCN, and the reaction is conducted as described in 2.1.6.A.

Method C: The chloroalkane (8 mmol) in DMF (10 ml) is stirred at *ca.* 10°C with TBA-F.3H₂O (7.6 g, 24 mmol) in DMF (10 ml) for 3 days. H₂O (25 ml) is added and the aqueous mixture is extracted with CH₂Cl₂ (3 × 10 ml). The organic extracts are washed well with H₂O, dried (MgSO₄) and evaporated. Fractional distillation of the residue yields the fluoroalkane. The more volatile fluoroalkanes are isolated by warming the CH₂Cl₂ solution of the product to *ca.* 45°C and 'blowing off' the fluoroalkane with dry N₂ into a cooled gas trap.

Method D: CsF (0.76 g, 5 mmol) and TBA-Br or Aliquat (5 mmol) [or TBA-F.3H₂O (1.6 g, 5 mmol)] are intimately mixed and the haloalkane or tosylate (2.5 mmol) is added. The mixture is heated for 4–40 h (Table 2.1) and the fluoro compound is isolated as described in 2.1.6.C.

2.1.7 Conversion of dichlorocyclopropanes into difluorocyclopropanes (Table 2.2)

The dichlorocyclopropane (8 mmol) in DMF (10 ml) is added dropwise to TBA-F.3H₂O (7.6 g, 24 mmol) in DMF (10 ml) at *ca.* 5°C. The exothermic reaction is stirred for *ca.* 4 h and then diluted with H₂O (250 ml) and extracted with CH₂Cl₂ (3 × 60 ml). The dried extracts are evaporated to yield the difluoro derivative.

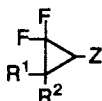
TABLE 2.1
Selected examples of the synthesis of aliphatic fluoro compounds

Starting material	Reaction conditions	% yield of fluoroalkane
<i>n</i> -C ₈ H ₁₇ Br	2.1.6.A/1 h/25 °C	35 ^a
	2.1.6.D/40 h/85 °C	77
<i>n</i> -C ₈ H ₁₇ OTos	2.1.6.B/1 h/25 °C	57 ^b
	2.1.6.D/40 h/85 °C	72 ^c
<i>n</i> -C ₆ H ₁₃ CHBrMe	2.1.6.A/1 h/25 °C	10 ^d
<i>n</i> -C ₆ H ₁₃ CHOTosMe	2.1.6.B/1 h/25 °C	52 ^e
BrCH ₂ CO ₂ Et	2.1.6.D/6 h/40 °C	80
PhCH ₂ Br	2.1.6.A/8 h/25 °C	66 ^f
Ph ₃ CCl	2.1.6.A/6 h/40 °C	65 ^g
CH ₂ =CHCH ₂ Br	2.1.6.A/5 min/25 °C	85
PhCOCl	2.1.6.A/1 h/25 °C	81

^a + 12% oct-1-ene and 40% octan-1-ol. ^b + traces of oct-1-ene and octan-1-ol. ^c + 10–20% oct-1-ene.

^d + 67% oct-1- and -2-ene. ^e 32% oct-1- and -2-ene and 7% octan-2-ol. ^f + 5% PhCH₂OH. ^g + 17% Ph₃COH.

TABLE 2.2
Selected examples of difluorocyclopropanes from dichlorocyclopropanes



R ¹	R ²	Z	% yield ^a
H	H	CO ₂ <i>t</i> -Bu	41 (35)
Me	H	CO ₂ CHMe ₂	46 (47)
Me	Me	CO ₂ CHMe ₂	40
H	H	COPh	41 (12)
H	H	SO ₂ Ph	43 (49)

^a using KF/TBA-HSO₄ in MeCN/H₂O at 80 °C over 8 h.

2.1.8 Conversion of dithioacetals into difluoroalkyl compounds

The dithioacetal (0.5 mmol) is added to TBA-H₂F₃ (0.45 g, 1.5 mmol) and *N*-iodosuccinimide (0.25 g, 1.1 mmol) in CH₂Cl₂ (1.5 ml) at –78 °C and the mixture is stirred and allowed to come to room temperature over 1 h. It is stirred for a further 1 h at room temperature and then poured into aqueous NaHSO₃ (sat. soln., 5 ml) and extracted with Et₂O (3 × 10 ml). The dried (Na₂SO₄) extracts are evaporated to yield the difluoroalkyl derivative.

Trimethylsilyl fluoride is obtained in 41% yield by a liquid:liquid two-phase reaction between trimethylsilyl chloride and potassium fluoride in the presence of

Aliquat [39]. The corresponding conversions of the chloride into the bromide or iodide are thermodynamically unfavourable.

2.1.9 Trimethylsilyl fluoride

Me_3SiCl (20 g, 0.18 mol) in PhCl (70 ml) is added to dry KF (10 g), Aliquat (0.31 g, 0.76 mmol) and H_2O (0.6 ml), and the mixture is stirred at $90\text{--}100^\circ\text{C}$ in an apparatus equipped with a cold trap at -50 to -60°C . After 1 h, KF (10 g) and H_2O (0.6 ml) are added and a similar addition is made after a further 2 h. Me_3SiF (6.9 g, 41%) b.p. $15\text{--}16^\circ\text{C}$ is collected in the cold trap.

Alkyl bromides have been converted into the corresponding iodides by treatment under solid:solid:liquid triphase conditions with silica-impregnated tetramethylammonium salts (*cf.* ester formation, Section 3.4) [40].

E-(β -Alkylvinyl)phenyliodonium salts react with tetra-*n*-butylammonium halides to yield the correspondingly substituted *Z*-haloethenes (80–100% for chloro-, bromo- and iodo-derivatives) [41]. In contrast, in the corresponding reaction with *Z*-(2-benzenesulphonyl-ethenyl)phenyliodonium salts, nucleophilic substitution occurs with retention of configuration to yield the *Z*-2-benzenesulphonyl-1-haloethenes [42]. The ammonium fluorides fail to yield the fluoroethenes, but produce the ethynes by simple elimination [41]. Where carboxylic acids have low solubility in organic solvents, their conversion into the acid chlorides is frequently difficult. Phase-transfer catalysis not only allows the conversion to be effected rapidly, it also results in high yields of a wide range of acid chlorides [43].

2.1.10 Conversion of carboxylic acids into the acid chlorides

SOCl_2 (208 g, 1.75 mol) is added in one portion to a refluxing solution of TEBA-Cl (0.27 g, 1.2 mmol) and the acid (0.826 mol) in $\text{Cl}(\text{CH}_2)_2\text{Cl}$ (1.5 l). The solution is refluxed for a further period of time, and then filtered hot and evaporated to yield the acid chloride, which is purified, if necessary, by chromatography from silica [e.g. *trans*-cyclohexane-1,4-dicarbonyl chloride (30 min), 96%; naphthalene-2,6-dicarbonyl chloride (12 h), 94%; biphenyl-4-carbonyl chloride (25 min), 60%; biphenyl-4,4'-dicarbonylchloride (16 h), 90%].

The conversion of acyl chlorides, sulphonyl chlorides and phosphoryl chlorides into the corresponding fluorides using potassium fluoride in the presence of a quaternary ammonium salt has been recorded [44–47]. Optimum yields are obtained when the 'dry' potassium fluoride contains *ca.* 1% water.

2.1.11 Acyl fluorides

The acyl chloride (0.2 mol), 'dry' KF (20 g) and TEBA-Cl (0.5 g, 2.2 mmol) are heated under reflux for *ca.* 10 h and the acyl fluoride is isolated by continuous distillation from the mixture [e.g. EtCOF , 70%; *t*- BuCOF , 70%; cyclo- $\text{C}_6\text{H}_{11}\text{COF}$, 94%; PhCH_2COF , 35%; PhCOF , 70%; EtOCO , 60%].

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2.2 NUCLEOPHILIC AROMATIC REACTIONS

In contrast with aliphatic nucleophilic substitution, nucleophilic displacement reactions on aromatic rings are relatively slow and require activation at the point of attack by electron-withdrawing substituents or heteroatoms, in the case of heteroaromatic systems. With non-activated aromatic systems, the reaction generally involves an elimination–addition mechanism. The addition of phase-transfer catalysts generally enhances the rate of these reactions.

Halogen exchange

Several examples are to be found in the patent literature for the exchange of chloro groups of activated chloroarenes by fluoro groups [1–5]. In the majority of procedures, anhydrous potassium fluoride and Aliquat are used in dimethyl sulphoxide at 170–175 °C. The reaction of 2-chloro-5-trichloromethylpyridine is catalysed by cetyltrimethylammonium bromide and yields 2-fluoro-5-trifluoromethylpyridine [2]. Only the 2- and 4-chloro groups of 2,4,5-trichloronitrobenzene are replaced to yield 5-chloro-2,4-difluoronitrobenzene (75%) [1]. 2,4-Dinitrochlorobenzene has been converted into the corresponding fluoro derivative using tetra-*n*-butylammonium fluoride, or tetra-*n*-butylammonium bromide/caesium fluoride, in moderate yield ~45% using a procedure analogous to **2.1.6.D** [7]. In contrast, with 1,2-dinitrobenzene and mononitrochlorobenzenes, it is the nitro group which is displaced by fluorine when they are reacted with ‘anhydrous’ tetra-*n*-butylammonium fluoride [7].

Bromoarenes are converted into the corresponding chloroarenes on treatment with sodium hypochlorite in the presence of a catalytic amount of nickel(II) tetraphenylporphyrin (NiTPP) and benzyltributylammonium bromide [8]. Fluoro and iodo substituents are not replaced. The reaction involves chlorine radical attack via the initial formation of a Ni(II)-OCl complex. Although high conversions are recorded, the procedure has not been extended for synthetic purposes.

Arenediazonium salts react with quaternary ammonium chlorides to yield chloroarenes in low yield (50%) [9].

2.2.1 Bromine–chlorine exchange reactions

Aqueous NaOCl (0.77 M, 7.8 ml) is added to the bromoarene (0.2 mmol), TBBA-Br (3 mg, 0.0084 mmol) and NiTPP (8 mg, 0.012 mmol) in CHCl₃ (6 ml) and stirred for 30 min at room temperature. The organic layer is then separated and filtered through a short column of alumina. Evaporation of the filtrate yields the chloroarene [e.g. PhCl 100%; 1,2-Cl₂C₆H₄, 85%; 1,4-Cl₂C₆H₄, 85%; 2-FC₆H₄Cl, 95%; 4-FC₆H₄Cl, 100%, 4-MeOC₆H₄Cl, 50%].

Synthesis of alkoxy and aryloxyarenes

Although many of the highly successful examples of phase-transfer catalysed reactions of activated haloarenes with alkoxide and phenoxide anions are catalysed by phosphonium salts or crown ethers, tetralkylammonium salts have also been used in reactions involving halonitrobenzenes [e.g. 10–28], haloanthraquinones [14, 25–27], halopyridines and haloquinolines [e.g. 29–35], haloacridines [36], haloquinazolines [37], halopyridazines and halopyridazinones [38, 39], halobenzoxazoles and halobenzothiazoles [40]. 2,6-Dichloropyridine reacts with oligo (ethylene)glycols in the presence of potassium carbonate and benzyltriethylammonium chloride to yield pyrido-crown ethers [41] in a manner analogous to the corresponding reactions of the pyridine acid chlorides (3.3.7.D).

Although yields for the synthesis of the aryl ethers can be very good, crown ethers and phosphonium salts are frequently considered to be the better catalysts, as the ammonium salts are more susceptible to decomposition under the strongly basic conditions at the higher temperatures required (tetra-*n*-butylammonium bromide is reported to have a half-life of only 7 minutes at 100°C in the presence of sodium phenoxide [42]), and reductive side reactions of the halonitrobenzenes leading to 4,4'-dihaloazoxybenzene and 4-haloaniline have also been noted [14]. In spite of these disadvantages, several patents describe the preparation of 4-nitroanisoles and 4-nitrophenetoles [e.g., 20–27] in exceptionally high yields (>95%). Activated fluoroarenes react more readily and require lower reaction temperatures than the chloro or bromo derivatives [12, 13, 15, 28]. Predictably primary alcohols are more reactive than secondary alcohols [13]; tertiary alcohols tend not to yield ethers, or only in low yield. The chloride ion, generated during the course of the nucleophilic reaction, acts as a catalyst poison, but careful adjustment of the alcohol and base concentrations obviates this problem [43].

Where reactivity is low, as for example with non-activated haloarenes, solid:liquid conditions are to be preferred over liquid:liquid conditions and better yields are frequently obtained when TDA-1 is used as the catalyst instead of a quaternary ammonium salt [28]. Although not activated to nucleophilic attack, 2-chlorophenol reacts with ethanol under solid:liquid conditions with microwave irradiation in the presence of benzyltrimethylammonium chloride to produce the ether in 70% yield [44]. It is possible that the procedure has potential for further exploitation.

2,3,4,5-Tetrabromopyridine reacts with 1,2-dihydroxybenzene to yield the dibromoazaphenoxane [34]. Tetra-*n*-butylammonium fluoride catalyses the conversion of 5-chloro-1-phenyltetrazole into tetrazol-5-yl glycosides, which are useful precursors for the formation of glycosyl fluorides [45].

2.2.2 Typical synthesis of alkoxy and aryloxyarenes from haloarenes

Method A: The activated haloarene (0.03 mol), TBA-Br (90 g, 0.28 mol) and KOH (17 g, 0.3 mol) in the appropriate alcohol (0.29 mol) are heated under reflux (see Table 2.3). The cooled reaction mixture is neutralized with dilute HCl, concentrated, and extracted with

TABLE 2.3
Selected examples of the formation of alkoxy- and aryloxyarenes

Haloarene	Alcohol/phenol	Reaction conditions	% yield
<i>Fluorobenzene</i>	PhCH ₂ OH	2.2.2.J/24 h/140°C	53
<i>1-Chloro-4-nitrobenzene</i>	EtOH	2.2.2.C/4 h/70–80°C	97
	<i>n</i> -C ₈ H ₁₇ OH	2.2.2.A/20 min/100°C	96
	MeCH(OH)Me	2.2.2.A/3 h/75°C	79 ^a
	MeCH(OH)Et	2.2.2.A/1.5 min/80°C	81
	PhOH	2.2.2.B/5 h/130°C	93
	4-NO ₂ C ₆ H ₄ OH	2.2.2.B/48 h/30°C	16 ^b
<i>1-Chloro-5-nitrobenzene</i>	4-ClC ₆ H ₄ OH	2.2.2.C/6.5 h/25°C	54
	4-EtC ₆ H ₄ OH	2.2.2.C/1.5 h/52°C	93
	4-MeOC ₆ H ₄ OH	2.2.2.C/4.25 h/50°C	74
	2,6-Me ₂ C ₆ H ₃ OH	2.2.2.C/2 h/50°C	84
	3,5-Me ₂ C ₆ H ₃ OH	2.2.2.C/15 min/56°C	76
<i>N-n-Butyl 2-chloro-5-nitrobenzamide</i>	EtOH	2.2.2.D/6 h/40°C	85
	<i>n</i> -C ₈ H ₁₇ OH	2.2.2.D/3 h/40°C	94
	MeCH(OH)Et	2.2.2.D/1.5 h/40°C	98
	PhCH ₂ OH	2.2.2.D/3 h/40°C	92
<i>Bis-(4-chloro-3-nitrophenyl)sulphone</i>	PhOH	2.2.2.E/16 h/rt	87
	4-PhOC ₆ H ₄ OH	2.2.2.E/24 h/rt	66
	4-MeC ₆ H ₄ OH	2.2.2.E/24 h/rt	94
	2-naphthol	2.2.2.E/24 h/rt	82
<i>2-Fluoropyridine</i>	PhOH	2.2.2.J/4 h/120°C	69
	PhCH ₂ OH	2.2.2.J/2 h/120°C	75
<i>2-Chloropyridine</i>	PhOH	2.2.2.J/4 h/120°C	10
	PhCH ₂ OH	2.2.2.J/2 h/120°C	85
<i>2-Bromopyridine</i>	PhOH	2.2.2.J/4 h/120°C	50
	PhCH ₂ OH	2.2.2.J/2 h/120°C	93
<i>2-Chloro-3-nitropyridine</i>	PhOH	2.2.2.C/1.25 h/25°C	84
	4-ClC ₆ H ₄ OH	2.2.2.C/4 h/25°C	64
	4-EtC ₆ H ₄ OH	2.2.2.C/1 h/50°C	84
	4-MeOC ₆ H ₄ OH	2.2.2.C/4.25 h/50°C	74
	2,6-Me ₂ C ₆ H ₃ OH	2.2.2.C/36 h/48°C	37
	3,5-Me ₂ C ₆ H ₃ OH	2.2.2.C/15 min/56°C	65
<i>2-Chloro-5-nitropyridine</i>	4-ClC ₆ H ₄ OH	2.2.2.C/6.5 h/25°C	54
	4-EtC ₆ H ₄ OH	2.2.2.C/1.5 h/50°C	93
	2,6-Me ₂ C ₆ H ₃ OH	2.2.2.C/2.0 h/50°C	84
	3,5-Me ₂ C ₆ H ₃ OH	2.2.2.C/15 min/56°C	76
<i>2-Chloro-3-cyanopyridine</i>	'A'	2.2.2.F/1 h/25°C	85 ^c

Haloarene	Alcohol/phenol	Reaction conditions	% yield
<i>2-Chloroquinoline</i>			
	PhOH	2.2.2.C/7 h/98 °C	60 ^d
	4-ClC ₆ H ₄ OH	2.2.2.C/6 h/98 °C	71 ^d
	4-MeC ₆ H ₄ OH	2.2.2.C/10 h/98 °C	98 ^d
	2,6-Me ₂ C ₆ H ₃ OH	2.2.2.C/6 h/98 °C	55 ^d
<i>4-Chloro-2-methylpyridazin-3-one</i>			
	'B'	2.2.2.I/2 h/85 °C	85 ^e
<i>5-Chloro-2-methylpyridazin-3-one</i>			
	'B'	2.2.2.I/2 h/85 °C	91 ^e
<i>4-Bromo-2-methylpyridazin-3-one</i>			
	'B'	2.2.2.I/2 h/85 °C	87 ^e
<i>5-Bromo-2-methylpyridazin-3-one</i>			
	'B'	2.2.2.I/2 h/85 °C	92 ^e
<i>4,5-Chloro-2-methylpyridazin-3-one</i>			
	'B'	2.2.2.I/2 h/85 °C	90 ^{e,f}
<i>4,5-Bromo-2-methylpyridazin-3-one</i>			
	'B'	2.2.2.I/2 h/85 °C	89 ^{e,g}

^a 21% using only 0.09 mol of TBA-Br. ^b + 66% 1-*n*-butoxy-4-nitrobenzene arising from reaction with the catalyst. ^c 3-cyano-2-(3-*t*-butylamino-2-dihydroxypropyloxy)pyridine isolated as fumarate salt. ^d using 1 mol equivalent of catalyst. ^e 2,3-dihydroxypropyloxy derivative. ^f bis ether + 8% mono ether. ^g bis ether + 6% mono ether.

'A', 3-*t*-butylamino-5-hydroxymethylloxazolidine. 'B', 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolidine.

CH₂Cl₂. The organic extracts are washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the aryl ether.

Method B: Powdered potassium phenoxide (39.5 g, 0.3 mol), the activated haloarene (0.03 mol), and TBA-Br (90 g, 0.28 mol) in PhCl (5 ml) are heated under reflux. The diaryl ether is isolated using the procedure described in Method A.

Method C: The phenol or alcohol (4.36 mmol) and aqueous NaOH (50%, 6 ml) are stirred at room temperature for *ca.* 1 h, and the activated haloarene (4.36 mmol) and TBA-Cl (0.14 g, 0.5 mmol) in PhMe (6 ml) are added. The mixture is stirred for 1–7 h (see Table 2.3), H₂O (50 ml) is then added and the mixture is extracted with CHCl₃ (3 × 30 ml). The organic extracts are washed with H₂O (3 × 30 ml), dried (Na₂SO₄), and evaporated to yield the aryl ether.

Method D: The alcohol (11.5 mol) is added to TBA-Br (0.32 g, 1 mmol) in aqueous NaOH (50%, 5 ml) and the mixture is stirred for 5 min. A suspension of the halonitrobenzamide (0.1 mol) in PhMe (150 ml) is then added and the two-phase system is stirred at 40 °C until the reaction is shown to be complete by TLC analysis. The mixture is cooled to room temperature and the organic phase is separated and evaporated. H₂O (300 ml) is added and the ether comes out of solution. (Method D fails with phenols and with secondary and tertiary alcohols.)

Method E: The halonitrophenyl sulphone (40 mmol) and TBA-Br (0.16 g, 0.5 mmol) in CH₂Cl₂ (100 ml) are added to a stirred solution of the phenol (20 mmol) in aqueous NaOH (40%, 100 ml) at room temperature. The two-phase system is stirred until the

reaction is complete and the aqueous phase is then separated and extracted with CH_2Cl_2 (50 ml). The combined organic solutions are washed with H_2O (3×75 ml), dried (Na_2SO_4), and evaporated to yield the aryl ether.

Method F: The 3-*t*-butyl-5-hydroxymethyl-2-phenyloxazolidine (0.8 mol) in PhMe (190 ml) is added slowly over *ca.* 0.5 h to the halopyridine (0.7 mol) and Aliquat (15.4 g, 38 mmol) in PhMe (1.5 l) and aqueous NaOH (50%, 1.4 l). The two-phase system is stirred for 1 h at 25°C and the aqueous phase is then separated and extracted with PhMe (350 ml). The organic solutions are washed with H_2O (2×400 ml) and extracted with HCl (1M, 2×725 ml). The pH of the aqueous extract is adjusted to 3.5 with solid potassium acetate and heated to 50°C for 3 h. The aqueous solution is washed with cyclohexane (2×300 ml), the pH is adjusted to 12 with aqueous NaOH (50%), and extracted with EtOAc (400 ml). The organic extract is dried (Na_2SO_4) and evaporated to yield the 3-*t*-butylamino-2-hydroxypropyloxy ether.

Method G (solid:liquid phase variation of Method F): The alcohol (0.059 mol) in PhMe (50 ml) is added at room temperature to the pyridine (0.086 mol) and Aliquat (1.2 g, 3 mmol) and KOH flakes (8.0 g) in PhMe (110 ml) and the mixture is stirred at 25°C for *ca.* 2 h. H_2O (50 ml) is then added and the organic phase is separated, washed with H_2O (2×25 ml), and extracted with HCl (1M, 2×75 ml). The product is worked up from the aqueous extract as described in Method F.

Method H: 4-Hydroxymethyl-2,2-dimethyl-1,3-dioxazolidine (0.06 mol) in PhCl (50 ml) is added to the haloarene (0.058 mol) and TBA-Br (0.97 g, 3 mmol) in PhCl (150 ml) and aqueous NaOH (20%, 60 ml). The mixture is stirred at room temperature for *ca.* 2 h and the aqueous phase is then separated and extracted with CH_2Cl_2 (3×10 ml). The organic solutions are washed well with H_2O , dried (Na_2SO_4), and evaporated to yield the ether.

Method I (solid:liquid variation of Method H): Powdered K_2CO_3 (5.6 g, 40 mmol) and TBA-Br (0.32 g, 1 mmol) are added to the dioxazolidine (10.5 mol) and the haloarene (10 mol) in MeCN (10 ml) and the suspension is stirred under reflux for 4–6 h. The mixture is then filtered and evaporated. The residue is taken up in CH_2Cl_2 (80 ml), and the solution is washed well with H_2O , dried (Na_2SO_4), and evaporated to yield the ether.

Method J (non-activated haloarenes): The alcohol (3 mmol) is added to crushed KOH (or *t*-BuOK) (3 mmol) and TDA-1 (0.3 mmol) and the mixture is stirred for 5–10 min at room temperature. The haloarene (2.5 mmol) is added and the mixture is heated at 140°C for *ca.* 24 h. The aryl alkyl ether is then worked up by chromatography on Florisil.

Method K. Under microwave irradiation: 2-Chlorophenol (0.26 g, 2 mmol), NaOH (80 mg), BTMA-Cl (46 mg, 0.2 mmol) and EtOH (1 ml) are subjected to microwave irradiation (700 W) in a sealed Pyrex tube for 2 min. The ether is isolated as described in Method J.

Fluoro- and chloroarenes activated by complexation with chromium tricarbonyl react readily with primary and secondary alcohols under basic conditions in the presence of a quaternary ammonium catalyst [46, 47]. Reaction of the chromium complexes with acetone oxime produces O-aryloximes in good yields (55–80%) [48].

2.2.3 Aryl ethers from haloarene chromium tricarbonyl complexes (Table 2.4)

Method A: The appropriate alcohol (1.77 mmol) is added to the complex (1.77 mmol), crushed KOH (0.3 g), and TOA-Br (0.27 g, 0.49 mmol) in PhH (25 ml) under N_2 and the

TABLE 2.4
Reaction of haloarene chromium tricarbonyl complexes $[\text{Cr}(\text{CO})_3\text{ArX}]$ with
alkoxide anions

ArX	ROH	Reaction conditions	% yield of ethers
1,2- $\text{Cl}_2\text{C}_6\text{H}_4$	MeOH	2.2.3.A/1 h/rt	80
	<i>i</i> -PrOH	2.2.3.A/6 h/45 °C	78
1,3- $\text{Cl}_2\text{C}_6\text{H}_4$	MeOH	2.2.3.A/30 min/rt	87 ^a
		2.2.3.B/20 h/45 °C	90 ^b
	<i>i</i> -PrOH	2.2.3.A/4 h/rt	69
1,4- $\text{Cl}_2\text{C}_6\text{H}_4$		2.2.3.B/20 h/45 °C	15 ^b
	MeOH	2.2.3.A/1 h/rt	70
	<i>i</i> -PrOH	2.2.3.A/4 h/45 °C	84

^a 85:15 ratio of mono- and dialkoxy compound. ^b 1,3-dialkoxybenzene.

reaction monitored by TLC. Upon completion of the reaction, the organic phase is separated, washed well with H_2O , dried (Na_2SO_4), and evaporated. The residue is taken up in the minimum amount of Et_2O , iodine (0.7 g, 2.75 mmol) is added, and the mixture is stirred at 0 °C for 2–3 h to decompose the complex and release the aryl ether.

Method B: As for Method B, except that 3.6 mmol of the alcohol is added and the reaction is conducted at 45 °C for *ca.* 20 h.

Nitroanisoles are also obtained by the catalysed displacement of a nitro group from dinitrobenzene. As expected, the 1,2- and 1,4-dinitrobenzenes are the more reactive, but 3-nitroanisole can be obtained in high yield after a prolonged reaction time [49].

2.2.4 Nitroanisoles from dinitrobenzenes

Sodium methoxide (75.5 g, 1.4 mol) in PhCl (200 ml), the dinitrobenzene (168 g, 1 mol) and Aliquat (20 g, 50 mmol) are stirred at 80 °C. When the reaction is complete the nitroanisole is isolated by steam distillation [e.g. from 1,2- $(\text{O}_2\text{N})_2\text{C}_6\text{H}_4$ (30 min); 79%; from 1,3- $(\text{O}_2\text{N})_2\text{C}_6\text{H}_4$ (8 h); 83% from 1,4- $(\text{O}_2\text{N})_2\text{C}_6\text{H}_4$ (5 min)].

There are relatively few reports of phase-transfer catalysed syntheses of phenols from activated haloarenes using quaternary ammonium salts, presumably because of the instability of the ammonium salts under the reaction conditions. A patented procedure for the conversion of, for example, 2,6-dichloropyridine into 6-chloropyrid-2-one (98%) using aqueous sodium hydroxide in the presence of benzyltriethylammonium chloride at 120–150 °C has been filed [32]. A possible route to the phenols, however, comes from the observed reaction of phenols with potassium carbonate:potassium hydrogen carbonate to yield the aryl carbonates (80–85%) using the procedure described for the preparation of dialkyl carbonates (3.3.13) [50].

Tetra-*n*-butylammonium dihydrogen trifluoride catalyses the reaction of activated chloroarenes with oxiranes (*cf.* 9.2.7) to yield 2-chloroethyl aryl ethers [51].

Synthesis of thioethers

Quaternary ammonium salts catalyse the reaction of activated halo benzenes with thioiminium salts [52], alkanethiols [10] and thiophenols [29, 53] to yield mixed thioethers and, with sodium sulphide under liquid:liquid or solid:liquid two-phase conditions, symmetrical diaryl sulphides [29, 54, 55] (Table 2.5).

TABLE 2.5
Selected examples of thioethers obtained from activated haloarenes

Haloarene	Product	% yield ^a
<i>Reaction with MeC(SMe)NH₂⁺Cl⁻</i>		
4-O ₂ NC ₆ H ₄ Cl	4-O ₂ NC ₆ H ₄ SMe	80 (8 h)
1,4-Cl ₂ C ₆ H ₄	1,4-(MeS) ₂ C ₆ H ₄	40 (8 h)
PhBr	PhSMe	40 (8 h)
<i>Reaction with MeC(SCH₂Ph)NH₂⁺Cl⁻</i>		
4-O ₂ NC ₆ H ₄ Cl	4-O ₂ NC ₆ H ₄ SCH ₂ Ph	80 (8 h)
4-ClC ₆ H ₄ CO ₂ H	4-PhCH ₂ SC ₆ H ₄ CO ₂ H	80 (8 h)
1,4-Cl ₂ C ₆ H ₄	1,4-(PhCH ₂ S) ₂ C ₆ H ₄	80 (8 h)
PhBr	PhSCH ₂ Ph	60 (8 h)
<i>Reaction with MeC(SCH₂CH=CH₂)NH₂⁺Cl⁻</i>		
4-O ₂ NC ₆ H ₄ Cl	4-O ₂ NC ₆ H ₄ SCH ₂ CH=CH ₂	85 (8 h)
1,4-Cl ₂ C ₆ H ₄	1,4-(CH ₂ =CHCH ₂ S) ₂ C ₆ H ₄	80 (8 h)
PhBr	PhSCH ₂ CH=CH ₂	65 (8 h)
<i>Reaction with PhSH</i>		
2-O ₂ NC ₆ H ₄ F	2-O ₂ NC ₆ H ₄ SPh	100 (30 min)
2-O ₂ NC ₆ H ₄ Cl	2-O ₂ NC ₆ H ₄ SPh	100 (1 h)
2-O ₂ NC ₆ H ₄ Br	2-O ₂ NC ₆ H ₄ SPh	100 (1.5 h)
2-O ₂ NC ₆ H ₄ I	2-O ₂ NC ₆ H ₄ SPh	100 (4 h)
4-O ₂ NC ₆ H ₄ F	4-O ₂ NC ₆ H ₄ SPh	100 (30 min)
4-O ₂ NC ₆ H ₄ Cl	4-O ₂ NC ₆ H ₄ SPh	100 (4.5 h)
4-O ₂ NC ₆ H ₄ Br	4-O ₂ NC ₆ H ₄ SPh	93 (4.5 h)
4-O ₂ NC ₆ H ₄ I	4-O ₂ NC ₆ H ₄ SPh	52 (4.5 h)
2,4-(O ₂ N) ₂ C ₆ H ₃ F	2,4-(O ₂ N) ₂ C ₆ H ₃ SPh	100 (15 min)
2,4-(O ₂ N) ₂ C ₆ H ₃ Cl	2,4-(O ₂ N) ₂ C ₆ H ₃ SPh	100 (30 min)

^a reaction time given in parentheses.

2.2.5 Alkyl aryl thioethers from thioiminium salts

Powdered KOH (0.17 g, 3 mmol) is added to the freshly prepared thioiminium halide [MeC(SR)NH₂⁺Cl⁻ or MeC(SR)NMe₂⁺Cl⁻] (3 mmol) and TEBA-Cl (0.12 g, 0.5 mmol) in CH₂Cl₂ (30 ml). The mixture is stirred at room temperature until the reaction is complete, as shown by TLC analysis. The organic phase is separated, washed with H₂O (2 × 25 ml), dried (Na₂SO₄), and the solvent evaporated under reduced pressure to yield the alkyl aryl thioether and the dialkyl disulphide, which can be separated by chromatography from silica.

2.2.6 Thioethers from thiophenols and thioalcohols

The thiophenol (60 mmol) and aqueous NaOH (10%, 100 ml) containing TBA-Br (0.96 g, 3 mmol) are stirred at room temperature and the haloarene (60 mmol) in PhMe (100 ml) is then added dropwise over 10 min. On completion of the reaction (1–4 h), as indicated by HPLC, the organic phase is separated, washed well with H₂O, dried (MgSO₄), and evaporated to yield the thioether.

2.2.7 Synthesis of diaryl sulphides

Aqueous NaHS (26%, 30 ml) is added over 3 h to the activated haloarene (0.1 mol), TBA-Br (3.2 g, 10 mmol), aqueous NaOH (16%, 40 ml) and PhCl (280 ml) at 97°C. The mixture is refluxed for *ca.* 4 h and then cooled to 70°C, filtered, and steam distilled to yield the diaryl sulphide.

The profitable conversion of thiuronium salts into dialkyl thioethers (see Section 4.1) is less successful for synthesis of diaryl thioethers. For example, 1-chloro-4-nitrobenzene reacts with bis-thiuronium salts of the type (H₂N)₂CS(CH₂)_nSC(NH₂)₂²⁺ under solid:liquid and liquid:liquid conditions to produce the desired bis-thioethers, ArS(CH₂)_nSAr, (20–35%), together with the diaryl sulphide, Ar₂S (5–15%). Higher yields of the diaryl sulphide are observed under liquid:liquid conditions whereas, under solid:liquid conditions, the diaryl disulphide, (ArS)₂, (20%) is also formed [56]. Diaryl disulphides are the sole products (>65%) from the stoichiometric reaction of aryl diazonium salts with benzyltriethylammonium tetrathiomolybdate [57].

2.2.8 Diaryl disulphides

The aryl diazonium tetrafluoroborate (4 mmol) is added portionwise over *ca.* 20 min to (TEBA)₂-MoS₄ (2.69 g, 4.4 mmol) in dry MeCN (10 ml) at 0°C. The mixture is stirred at 0°C for 1 h and then at 25°C for *ca.* 5 h. The solvent is removed under reduced pressure and the residue is extracted with Et₂O (5 × 30 ml). The ethereal extracts are evaporated and the product purified by chromatography from silica to yield the diaryl disulphide.

Haloarene chromium tricarbonyl complexes are activated to nucleophilic attack by thiolate anions [58, 59]. High yields of the thioethers are obtained under liquid:liquid two-phase conditions, but optimum yields are achieved under solid:liquid conditions. In many cases the thioether is produced directly but, where the reaction mixture contains thioether and its chromium complex, the thioether can be isolated by degradation of the complex with iodine or an excess of the thiol. Both 1,2- and 1,4-dichlorobenzenes yield only monothioethers, even when an excess of thiolate anion is used. In contrast, 1,3-dichlorobenzenes produce a mixture of the mono- and dithioethers [59]. Aryl allyl thioethers have been produced under catalysed Heck reaction conditions from *S*-allyl thiocarbamates and iodobenzene [60].

2.2.9 Thioethers from haloarene chromium tricarbonyl complexes (Table 2.6)

Method A: Aqueous NaOH (50%, 25 ml) and the catalyst (0.6 mmol) are added to the complex (2.15 mmol) and thiol (2.37 mmol) in PhH (25 ml) under N₂. The mixture is stirred and the reaction monitored by TLC. Upon completion of the reaction, the organic phase is separated, washed well with H₂O, dried (Na₂SO₄), and evaporated. The residue is taken up in the minimum amount of Et₂O, I₂ (0.7 g, 2.75 mmol) is added, and the mixture is stirred at 0°C for 2–3 h. The thioether is purified by fractional distillation.

Method B: The complex (2.15 mmol) and thiol (2.37 mmol) in PhH (25 ml) are added to crushed NaOH (0.26 g) and the catalyst (0.6 mmol) under N₂. The mixture is stirred and the reaction monitored by TLC. The thioether is isolated as described in Method A.

Activated haloarenes react with potassium thiocyanate under the influence of a quaternary ammonium salt to form the corresponding aryl thiocyanates [61]. Aliquat is preferred over tetra-*n*-butylammonium bromide for the reactions of fluoro- and iodoarenes but, in all cases, yields are extremely high.

2.2.10 Aryl thiocyanates

The activated haloarene (25 mmol) in PhMe (12 ml) is stirred with aqueous NaSCN (50%, 10 ml) and TBA-Br or Aliquat (1 mmol) at 90°C for *ca.* 2 h. The aqueous phase is

TABLE 2.6
Selected examples of the reaction of haloarene chromium tricarbonyl complexes
[Cr(CO)₃ArX] with thiolate anions

ArX	RSH	Reaction conditions	Yield %
PhF	MeSH	2.2.9.A/30 min/rt	88
	<i>n</i> -BuSH	2.2.9.A/28 min/rt	90
	<i>i</i> -PrSH	2.2.9.A/28 min/rt	95
	<i>t</i> -BuSH	2.2.9.A/1 h/rt ^{a,b}	97
PhCl	<i>n</i> -BuSH	2.2.9.A/1.5 h/rt	90
	<i>i</i> -PrSH	2.2.9.A/35 min/rt	92
	<i>t</i> -BuSH	2.2.9.A/2 h/45°C ^{b,c}	94
		2.2.9.B/45 min/45°C ^b	>98
3-MeC ₆ H ₄ Cl	<i>t</i> -BuSH	2.2.9.B/27 min/60°C ^d	>98
4-MeC ₆ H ₄ Cl	<i>t</i> -BuSH	2.2.9.B/30 min/60°C ^b	>98
1,2-Cl ₂ C ₆ H ₄	MeSH	2.2.9.B/15 min/rt	72
	<i>n</i> -BuSH	2.2.9.B/40 min/rt	91 ^e
	<i>t</i> -BuSH	2.2.9.B/1 h/rt	97
1,3-Cl ₂ C ₆ H ₄	MeSH	2.2.9.B/40 min/rt	86 ^f
	<i>n</i> -BuSH	2.2.9.B/6 min/rt	77 ^g
	<i>t</i> -BuSH	2.2.9.B/3 h/rt	77 ^h
1,4-Cl ₂ C ₆ H ₄	MeSH	2.2.9.B/15 min/rt	65
	<i>n</i> -BuSH	2.2.9.B/15 min/rt	58 ^e

^a using TOA-Br. ^b using Aliquat. ^c using CTA-Cl. ^d using Aliquat at 60°C over 6 h. ^e complex destroyed by the addition of a further 1.77 mmol of the thiol. ^f 84 : 16 ratio of monothioether:dithioether. ^g 7 : 3 ratio of monothioether:dithioether. ^h 78 : 22 ratio of monothioether:dithioether.

separated, extracted with PhMe (2 × 25 ml) and the combined organic solutions are evaporated to yield the aryl thiocyanate [e.g. 98.8% 2,4-(O₂N)₂C₆H₃SCN from 2,4-(O₂N)₂C₆H₃F; 99.9% from 2,4-(O₂N)₂C₆H₃Cl; 100% from 2,4-(O₂N)₂C₆H₃Br after 1 h; 100% from 2,4-(O₂N)₂C₆H₃I after 1 h].

The yields of arenesulphonic acids (~80%) via the reaction of activated haloarenes with potassium sulphite under phase-transfer catalytic conditions [62, 63] are no better than conventional non-catalytic methods, although reaction conditions are less severe. There is evidence that indicates the initial attack by the sulphite anion is at C-5. Surprisingly, tri-*n*-butylamine is a better catalyst, producing higher yields (>90%).

2.2.11 Arenesulphonic acids

KOH (2.8 g) and K₂SO₃ (8.1 g) in H₂O (25 ml) is added to the activated chloroarene (25 mmol) and TBA-HSO₄ (17.3 g, 50 mmol) in CH₂Cl₂ (50 ml), which immediately becomes blue-red. The mixture is refluxed for 1 h. The organic phase is separated, Ba(ClO₄)₂ (12 g) in H₂O (15 ml) is added, and the mixture is stirred to precipitate the barium salt of the sulphonic acid, which is washed with CH₂Cl₂ (10 ml) and dried over P₂O₅.

Synthesis of aminoarenes

Anilines, aliphatic amines, and ammonia react with electron-deficient halobenzenes and haloheteroarenes to produce the expected amino derivatives in good yield (Table 2.7) [37, 64–67].

TABLE 2.7
Selected examples of the reaction of π -deficient haloarenes with amines

Haloarene	Amine	Reaction conditions	% yield
2,4-(O ₂ N) ₂ C ₆ H ₃ Cl	NH ₃	2.2.12.A/24 h	~100
	NH ₃	2.2.12.B/20 h	95
2-O ₂ N-4-CF ₃ C ₆ H ₃ Cl	4-O ₂ NC ₆ H ₄ NH ₂	2.2.12.C/6 h	84
4-Bromopyridine	pyrrolidine	2.2.12.D/5 h	67
	piperidine	2.2.12.D/5 h	67
	morpholine	2.2.12.D/5 h	68

2.2.12 Reaction of π -deficient haloarenes with ammonia and amines

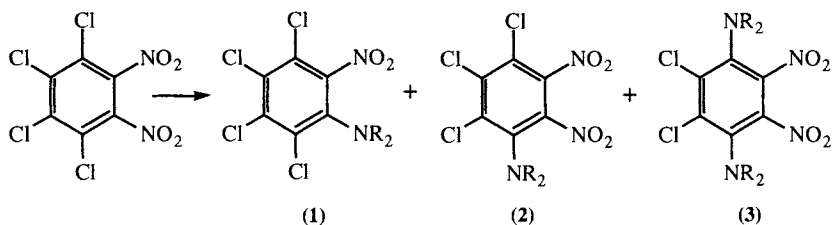
Method A: NH₃ is bubbled at 10 ml/min through a solution of haloarene (10 mmol) and TBA-Br (0.32 g, 1 mmol) in PhMe (5 ml) at room temperature and the reaction is monitored by GLC. After *ca.* 24 h, H₂O (10 ml) and CH₂Cl₂ (10 ml) are added and the organic phase is separated, washed well with brine and H₂O, dried (MgSO₄), and evaporated to yield the aminoarene.

Method B: Aqueous NH_3 (25%, 5 ml), TBA-Br (0.32 g, 1 mmol) and the haloarene (10 mmol) in PhMe (5 ml) are stirred at 70°C for *ca.* 20 h. The product is worked up as in Method A.

Method C: Aqueous NaOH (53%, 4 ml) is added to the haloarene (2.27 mmol), amine (5.11 mmol) and TBA-Br (0.1 g, 0.32 mmol) in MeCN (5 ml) and the mixture is stirred at 40°C for 6 h. The solution is neutralized with aqueous NH_4Cl and extracted with CH_2Cl_2 (3×10 ml). The dried (MgSO_4) extracts are evaporated to yield the diarylamine, which is purified by chromatography.

Method D: 4-Halopyridinium chloride (0.01 mol) is added to aqueous NaOH (50%, 5 ml), followed by an excess of the secondary amine (*ca.* 5 ml) and TEBA-Br or TBA-Br (0.01 mol), and the mixture is stirred at 100°C for 5 h (with the more volatile amines, further additions may be necessary during the course of the reaction). Excess amine is removed by distillation and H_2O (25 ml) is added. The aqueous mixture is extracted with PhH (4×25 ml) and the combined extracts are dried (Na_2SO_4), and evaporated under reduced pressure to yield the aminopyridine. Low yields and by-products are obtained from the reaction with 2-chloropyridine.

1,2,3,4-Tetrachloro-5,6-dinitrobenzene reacts with primary amines to yield 2,3,4,5-tetrachloro-6-nitroanilines through selective displacement of a nitro group, and with secondary amines to give similar products, together with trichlorodinitroanilines and dichlorodinitrophenylenediamines (Scheme 2.1). Overall conversion is generally higher than that observed in the absence of the catalyst and the addition of the quaternary ammonium salt shifts selectivity in favour of displacement of a chloro group (Table 2.8). It has been proposed that a complex cation is produced between the amine and ammonium cation, which has the twofold effect of making the amine more lipophilic and effectively increasing its bulk thereby sterically hindering displacement of the nitro group.



Scheme 2.1

2.2.13 Reaction of 1,2,3,4-tetrachloro-5,6-dinitrobenzene with amines

Aliquat (0.2 g, 0.5 mmol) is added to the amine (14.5 mmol) in H_2O (25 ml) and 1,2,3,4-tetrachloro-5,6-dinitrobenzene (2.0 g, 6.5 mmol) in PhMe (25 ml). The two-phase system is stirred under reflux for *ca.* 1 h and then cooled. The organic phase is separated, dried (MgSO_4), and evaporated. Chromatography of the residue from silica gives the aniline.

TABLE 2.8
Selected examples of the reaction of 1,2,3,4-tetrachloro-5,6-dinitro-
benzene with amines

Amine	% yield (see Scheme 2.2) ^a		
	1	2	3
<i>n</i> -BuNH ₂	80 (78)	0 (0)	0 (0)
<i>t</i> -BuNH ₂	75 (0)	0 (0)	0 (0)
Me ₂ NH	25 (41)	51 (18)	0 (0)
Et ₂ NH	0 (0)	65 (22)	0 (0)
Pyrrolidine	63 (53)	16 (0)	0 (0)
Piperidine	21 (31)	61 (37)	7 (2)
Morpholine	0 (0)	60 (1)	0 (4)

^a % yields in absence of catalyst are given in parentheses.

Several examples of the *N*-arylation of azoles by activated haloarenes under phase-transfer catalysed conditions have been reported (see Chapter 5). The reaction is often aided by the use of ultrasound in the absence of a solvent [e.g. 68].

The nucleophilic displacement of the halogen from 2,4-dinitrohalobenzenes by azide ion is catalysed by macrotricyclic ammonium salts [69]. Kinetic studies indicate that the azide ion is entrapped and transported within the macrocyclic cage. The highly explosive tetra-azido-*p*-benzoquinone is obtained when the tetrachloroquinone is reacted with an excess of sodium azide under phase-transfer catalytic conditions [70]. When only a twofold excess of the azide is used, the 2,5-diazido-3,6-dichloro compound is obtained.

Reaction of activated haloarenes with cyanide and carbanions

Nitrobenzenes react with potassium cyanide in the presence of cetyltrimethylammonium bromide to yield benzonitriles [71]. The reaction also requires the presence of chloro substituents on the ring and at least two nitro groups (Table 2.9). Diazosulphides, ArN=NSPh, are converted into the benzonitriles, ArCN, by a photochemically induced S_{RN}1 reaction with tetra-*n*-butylammonium cyanide [72, 73]. Yields vary from <20% to >70%. Photocyanation of aromatic hydrocarbons has been achieved using tetra-*n*-butylammonium cyanide in acetonitrile or dichloromethane [74, 75].

2,3-Dichloroanthaquinones have also been converted into the corresponding dicyano derivative, via what has been claimed to be the disulphonic acid (*vide supra*) [76]. Chloropurines have been converted into the corresponding cyano compounds using tetraethylammonium cyanide [77].

2.2.14 Benzonitriles from nitrobenzenes

The nitrobenzene (32 mmol) in CHCl₃ (33 ml) is heated under reflux with CTMA-Br (0.4 g, 1.1 mmol) and KCN (4.4 g, 67 mmol) in H₂O (33 ml). When the reaction is

complete, as shown by GLC, the mixture is extracted with CH_2Cl_2 (3×30 ml) and the combined organic solutions are washed well with brine, dried (MgSO_4), and evaporated. The residue is taken up in Et_2O , filtered, and evaporated to yield the nitrile.

TABLE 2.9
Benzonitriles from nitrobenzenes

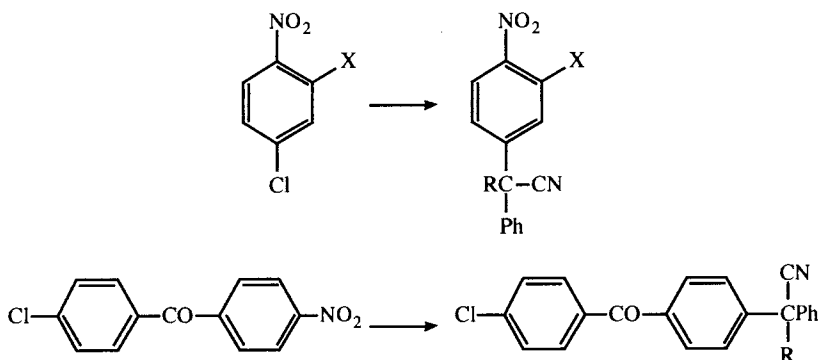
Nitrobenzene	Product	% yield
1,2-(O_2N) $_2\text{C}_6\text{Cl}_4$	1,2-(CN) $_2\text{C}_6\text{Cl}_4$	53
	1-CN-2- $\text{O}_2\text{NC}_6\text{Cl}_4$	2
1,3-(O_2N) $_2\text{C}_6\text{Cl}_4$	1-CN-3- $\text{O}_2\text{NC}_6\text{Cl}_4$	30
1,4-(O_2N) $_2\text{C}_6\text{Cl}_4$	1,4-(CN) $_2\text{C}_6\text{Cl}_4$	79
	1-CN-4- $\text{O}_2\text{NC}_6\text{Cl}_4$	4
1,4-(O_2N) $_2\text{C}_6\text{H}_4$	—	0
$\text{C}_6(\text{NO}_2)\text{Cl}_5$	—	0

2.2.15 Benzonitriles from aryldiazosulphides

The aryldiazosulphide* $\text{ArN}=\text{NSPh}$ (1.3 mmol) in DMSO (50 ml) is stirred under Ar with TBA-CN (1.75 g, 6.5 mmol) in DMSO (50 ml) and the solution is irradiated with 'tungsten' light until the evolution of N_2 ceases. Brine (150 ml) is added and the mixture is extracted with Et_2O (4×50 ml). The ethereal extracts are washed with aqueous NaOH (10%, 50 ml) and brine (50 ml), dried (Na_2SO_4), and evaporated to yield the benzonitrile (30–70%). *The diazosulphides are potentially EXPLOSIVE.

The nucleophilic displacement reaction of the chloro group of chloronitrobenzenes [78], chloronitropyridines [29, 79] and their 1-oxides [80] with phenylacetonitriles under liquid:liquid two-phase conditions is catalysed by tetra-*n*-butylammonium chloride or benzyltriethylammonium chloride to give the substituted acetonitriles in moderate to good yields (43–87%) (Table 2.10). The analogous reaction with 4-chloro-4'-nitrobenzophenones leads to displacement of the nitro group (Scheme 2.2) [78]. Similarly, the nitro group of 3-chloro-4-nitrobenzophenone is displaced by phenylacetonitrile anions, but the corresponding reaction with 5-chloro-2-nitrobenzophenone results in displacement of the chloro group [81]. Electron transfer processes have also been observed with the formation of 1,2-dicyano-1,2-diphenylethanes and azoxybenzenes [78]. The reaction of phenylacetonitrile with activated haloarenes is generally more effectively conducted under solid:liquid phase-transfer catalytic conditions [28]. Activated 2-chloropyridines react with phenylacetonitriles under liquid:liquid two-phase conditions, but simple 2-halopyridines produce the 2-(2-pyridyl)acetonitriles only under the solvent free solid:liquid conditions [35].

Phenylpropanones react with 2- and 4-nitro- and 2,4-dinitrochlorobenzenes with displacement of the chloro group under phase-transfer catalysed conditions analogous to those involving phenylacetonitriles [82].



Scheme 2.2

TABLE 2.10

Selected examples of the reaction of activated haloarenes with phenylacetonitriles^a

Activated arene	PhCH(CN)R	Product	% yield
2-ClC ₆ H ₄ NO ₂	R = Me	2-[PhC(Me)(CN)]C ₆ H ₄ NO ₂	80
	Et	2-[PhC(Et)(CN)]C ₆ H ₄ NO ₂	95
	CH ₂ Ph	2-[PhCH ₂ C(Ph)(CN)]C ₆ H ₄ NO ₂	88
	Ph ^b	2-[Ph ₂ C(CN)]C ₆ H ₄ NO ₂	88
4-ClC ₆ H ₄ NO ₂	R = H	4-NO ₂ C ₆ H ₄ CH(Ph)CN	80 ^c
	Me	4-[PhC(Me)(CN)]C ₆ H ₄ NO ₂	92
	Et	4-[PhC(Et)(CN)]C ₆ H ₄ NO ₂	95
	CH ₂ Ph	4-[PhCH ₂ C(Ph)(CN)]C ₆ H ₄ NO ₂	87
	Ph	4-[Ph ₂ C(CN)]C ₆ H ₄ NO ₂	71
2,4-Cl ₂ C ₆ H ₃ NO ₂	R = Me	2-Cl-4-[PhC(Me)(CN)]C ₆ H ₃ NO ₂	82
	Et	2-Cl-4-[PhC(Et)(CN)]C ₆ H ₃ NO ₂	78
3,4-Cl ₂ C ₆ H ₃ NO ₂	R = H	4-Cl-2-[PhC(Et)(CN)]C ₆ H ₃ NO ₂	3
	Me	3-Cl-4-[PhC(Me)(CN)]C ₆ H ₃ NO ₂	92
	Et	3-Cl-4-[PhC(Et)(CN)]C ₆ H ₃ NO ₂	61
	PhCH ₂	3-Cl-4-[PhC(PhCH ₂)(CN)]C ₆ H ₃ NO ₂	82
2,5-Cl ₂ C ₆ H ₃ NO ₂	R = Me	3-Cl-4-[Ph ₂ C(CN)]C ₆ H ₃ NO ₂	90
	Et	5-Cl-2-[PhC(Me)(CN)]C ₆ H ₃ NO ₂	85
	PhCH ₂	5-Cl-2-[PhC(PhCH ₂)(CN)]C ₆ H ₃ NO ₂	98
	Ph	5-Cl-2-[Ph ₂ C(CN)]C ₆ H ₃ NO ₂	93
2,4-(O ₂ N) ₂ C ₆ H ₃ Cl	R = H	2-4-(O ₂ N) ₂ C ₆ H ₃ CH(Ph)CN	88 ^c
	Me	2,4-(O ₂ N) ₂ C ₆ H ₃ [CPh(Me)(CN)]	78
	Et	2,4-(O ₂ N) ₂ C ₆ H ₃ [CPh(Et)(CN)]	61
	PhCH ₂	2-4-(O ₂ N) ₂ C ₆ H ₃ [CPh(PhCH ₂)(CN)]	86
	Ph	2-4-(O ₂ N) ₂ C ₆ H ₃ [CPh ₂ (CN)]	91
2-Cl-5-(O ₂ N)C ₅ H ₃ N ^d	R = Et	2-[PhC(Me)(CN)]-5-(O ₂ N)C ₅ H ₃ N	51
	Ph	2-[Ph ₂ C(CN)]-5-(O ₂ N)C ₅ H ₃ N	87
	OMe	2-[PhC(OMe)(CN)]-5-(O ₂ N)C ₅ H ₃ N	43
4-[4-ClC ₆ H ₄ CO]C ₆ H ₄ NO ₂ ^e	R = Me	4-[4-ClC ₆ H ₄ CO]C ₆ H ₄ [CPh(Me)(CN)]	75
	Et	4-[4-ClC ₆ H ₄ CO]C ₆ H ₄ [CPh(Et)(CN)]	70
	PhCH ₂	4-[4-ClC ₆ H ₄ CO]C ₆ H ₄ [CPh(PhCH ₂)(CN)]	67

^a Method 2.2.16.A. ^b Reaction conducted in DMSO. ^c Method 2.2.16.B. ^d Method 2.2.18.A. ^e Method 2.2.17.

Direct coupling of carbon nucleophiles with 1,3-dinitrobenzene is promoted by ultraviolet irradiation in the presence of quaternary ammonium fluorides, which can act not only as the base to generate the carbon nucleophile, but also as a proton transfer agent in the rearomatization step [83]. The dinitrobenzene acts as the electron acceptor in the photochemical step. No reaction occurs in the absence of the fluoride and, surprisingly, although simple ketones, nitriles, esters and β -keto esters react, pentan-2,4-dione does not.

2.2.16 Diarylacetonitriles

Method A: Aqueous NaOH (50%, 15 ml) is added portionwise to the appropriate phenylacetonitrile (50 mmol), the chloronitrobenzene (50 mmol), and TEBA-Cl (0.23 g, 1 mmol) in PhH (10 ml) (the solvent can be omitted with liquid chloronitrobenzenes). The mixture is stirred vigorously at 40–50°C for 3–4 h and then diluted with H₂O (25 ml). The aqueous phase is separated, extracted with PhH (2 \times 10 ml), and the combined PhH solutions are dried (MgSO₄) and evaporated to yield the product.

Method B: PhCH₂CN (0.35 g, 3 mmol) is added to crushed KOH (0.17 g) and Aliquat (0.12 g, 0.3 mmol) and the mixture is stirred for *ca.* 10 min before the addition of the activated chloroarene (2.5 mmol). The mixture is stirred at 80°C for 1 h (30 min at 20°C for 2,4-dinitrochlorobenzene) and then filtered through a pad of Florisil. The Florisil is washed with Et₂O (25 ml) and the combined organic solutions are dried (MgSO₄) and evaporated to yield the diarylacetonitrile.

2.2.17 Reaction of 4-chloro-4'-nitrobenzophenone with phenylacetonitriles

The benzophenone (2.7 g, 15 mmol), the appropriate phenylacetonitrile, and TEBA-Cl (0.1 g, 0.4 mmol) are stirred with aqueous NaOH (50%, 10 ml) at 50–60°C for 3 h. The product is isolated as described in 2.2.16.

2.2.18 2-(2-Pyridyl)phenylacetonitriles

Method A (liquid:liquid system): The 2-chloropyridine (10 mmol) in PhH is stirred with the appropriate phenylacetonitrile (10 mmol), TBA-Cl (0.28 g, 1 mmol) and aqueous NaOH (50%, 10 ml) at 50°C. On completion of the reaction (0.5–2.5 h), the organic phase is separated, washed well with H₂O, dried (MgSO₄), and evaporated to yield the pyridylacetonitrile, which can be purified by chromatography.

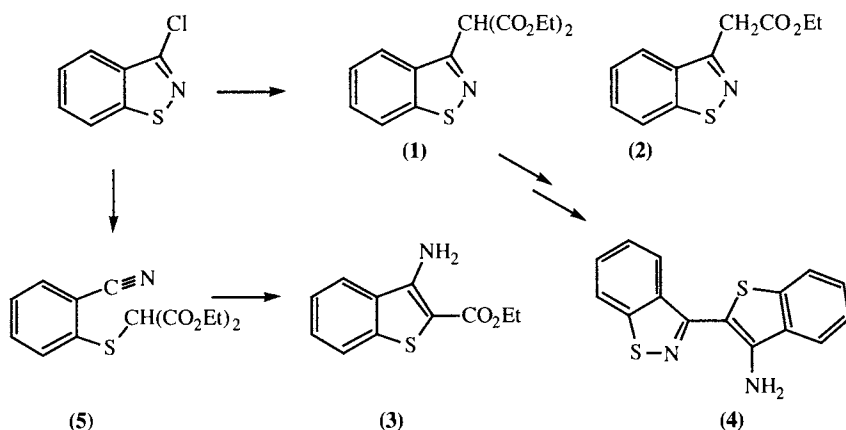
Method B (solid:liquid system): The phenylacetonitrile (3 mmol) is added to powdered KO^tBu (0.67 g, 6 mmol) and Aliquat (73 mg, 0.18 mmol) and the mixture is mixed thoroughly. The 2-halopyridine (4.5 mmol) is added and the mixture is stirred at 85 or 120°C for 1–2 h. CH₂Cl₂ (50 ml) is added and the organic solution is filtered through a pad of Florisil to yield, on evaporation of the solvent, the pyridylacetonitrile (Table 2.11).

In contrast with the reaction of the chloropyridine, but in keeping with its observed reactions with diethyl malonate under 'classical' procedures, 3-chloro-1,2-benzisothiazole produces not only the S_NAr products, (1) and (2) (Scheme 2.3), but also products arising under the basic conditions from ring opening of the isothiazole

TABLE 2.11
Selected examples of the solid:liquid reaction of 2-halopyridines with
phenylacetonitriles

Halopyridine	PhCHRCN	Reaction conditions	% yield
2-Fluoropyridine	R = Ph	2 h/120°C	5
2-Chloropyridine	H	1 h/85°C	47
	Me	1 h/85°C	46
	Ph	2 h/120°C	41
2-Bromopyridine	H	1 h/85°C	52
	Ph	2 h/120°C	52

ring with loss of the chloride ion and subsequent ring closure incorporating the malonate residue [84]. The course of the reaction (Scheme 2.3) and the relative yields of the products depends on the choice of solvent, and the concentration of the catalyst. In the absence of an added solvent and approximately molar equivalent of the catalyst, the S_NAr product (**1**) predominates (59%) with (**2**) (11%) and (**3**) (17%). When hexane is used as a solvent, (**3**) predominates (92%) with 8% of (**2**) and, in xylene, the precursor (**5**) (75%) and (**3**) (24%) are produced. With a catalytic amount (0.01 molar equivalent) of the catalyst and 50% aqueous sodium hydroxide, (**4**) is the major product (67%) with (**3**) (23%).



Scheme 2.3

2.2.19 Reaction of 3-chloro-1,2-benzisothiazole with diethyl malonate

TBA-Br (0.8 g, 2.5 mmol) in aqueous NaOH (6%, 3 ml) is added to $\text{CH}_2(\text{CO}_2\text{Et})_2$ (0.32 g, 2.5 mmol) and 3-chloro-1,2-benzisothiazole (0.21 g, 1.25 mmol) and the mixture is heated under reflux for 3 h. The reaction mixture is extracted with CH_2Cl_2 (2

× 25 ml), the extracts are washed well with H₂O, dried (MgSO₄), and evaporated to yield the products (1)–(3). In the catalytic process, on completion of the reaction, the reaction mixture is diluted with H₂O to cause precipitation of (4).

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2.3 ELECTROPHILIC HALOGENATION AND RELATED REACTIONS

Free halogens are generally inconvenient to use, owing to their toxic and corrosive nature, but can be replaced by quaternary ammonium polyhalides. Quaternary ammonium tribromides are well established [e.g. 1] as solid, readily handled and relatively non-toxic alternatives for electrophilic bromine. More recently, other quaternary ammonium polyhalides have been produced, which together with the tribromides, have wide application as catalysts or in stoichiometric quantities in electrophilic substitution and addition reactions, oxidations, etc.

2.3.1 Quaternary ammonium tribromides

Method A: Aqueous HBr (47%, 7 ml) is added to the quaternary ammonium bromide (30 mmol) and NaBrO₃ (1.5 g, 10 mmol) in H₂O (60 ml) and the mixture stirred at room temperature. The orange precipitate is collected and recrystallized from CH₂Cl₂/Et₂O [TBA-Br₃, 95%, m.p. 84 °C; TMBA-Br₃, 78%, 100–101 °C].

Method B: TMBA-Br (23 g, 0.1 mol) in H₂O (100 ml) is added to Br₂ (15.98 g, 0.1 mol) in CH₂Cl₂ (100 ml) and the mixture is stirred at room temperature for 30 min. The organic phase is separated, dried (MgSO₄), and evaporated to yield TMBA-Br₃.

Method C: Br₂ (16 g, 0.1 mol) is added to TBA-Br (32.2 g, 0.1 mol) in MeCN (150 ml) and the solution is stirred for 30 min at room temperature. Evaporation of the solvent under reduced pressure yields TBA-Br₃ (96%).

2.3.2 Benzyltrimethylammonium dibromochlorate

TMBA-Cl (18.6 g, 0.1 mol) in H₂O (100 ml) is added dropwise to Br₂ (15.98 g, 0.1 mol) in CH₂Cl₂ (100 ml) and the mixture is stirred at room temperature for 30 min. The organic phase is separated, dried (MgSO₄), and evaporated to yield TMBA-ClBr₂ (71%), m.p. 101–102 °C.

2.3.3 Benzyltrimethylammonium dichloroiodate

TMBA-Cl (18.6 g, 0.1 mol) in H₂O (100 ml) is added dropwise to ICl (16.2 g, 0.1 mol) in CH₂Cl₂ (200 ml) and the mixture is stirred at room temperature for 30 min. The organic phase is separated, dried (MgSO₄), and evaporated to yield TMBA-ICl₂ (86%), m.p. 125–126 °C.

2.3.4 Benzyltrimethylammonium tetrachloroiodate

Method A: Cl₂ is bubbled through a stirred solution of BTMA-Cl (18.6 g, 0.1 mol) and I₂ (12.7 g, 0.05 mol) in CH₂Cl₂ (250 ml) over a period of ca. 30 min. The precipitated

TMBA-ICl₄ is collected and dried in air, m.p. 106–125°C (decomp.). The salt loses Cl₂ above 106°C and the final m.p. is that of TMBA-ICl₂.

Method B: Cl₂ is bubbled through a stirred solution of BTMA-ICl₂ (34.8 g, 0.1 mol) in CH₂Cl₂ (300 ml) over a period of *ca.* 30 min and the precipitated tetrachloroiodate salt is collected by filtration.

Method C: TMBA-Cl (18.6 g, 0.1 mol) is added portionwise with stirring to ICl₃ (23.3 g, 0.1 mol) in CH₂Cl₂ (300 ml) over a period of *ca.* 30 min at room temperature. Over this time, the tetrachloroiodate salt is precipitated.

2.3.5 Tetra-*n*-butylammonium tetrachloroiodate

Cl₂ is passed through a solution of TBA-I (200 g, 0.54 mol) in CHCl₃ (1.5 l) at 0°C until the original colour has turned through deep red to orange–yellow and the TBA-ICl₄ salt precipitates. The mixture is warmed at 100°C for *ca.* 10 min to remove excess Cl₂ and then cooled to 0°C and the product collected, m.p. 137–139°C.

Quaternary ammonium tribromides can also be produced *in situ* from the quaternary ammonium bromide, sodium hypochlorite and sodium bromide and can be used, for example, in electrophilic addition reactions reaction with alkenes and alkynes.

Alkenes are converted in high yield by the preformed ammonium tribromides into the corresponding dibromoalkanes [2,3].

1,2-Disubstituted alkynes and terminal alkynes form *E*-dibromoalkenes [4]; when the tribromide is formed *in situ* in an essentially basic medium, an addition reaction followed by elimination of hydrogen bromide results in the conversion of terminal alkynes into the 1-bromoalkynes [5]. When the addition reaction is conducted in methanol, 1,1-dibromo-2,2-dimethoxyalkanes are produced, in addition to the 1,2-dibromoalkenes [6]. The dimethoxy compounds probably result from the initial intermediate formation of bromomethoxyalkenes. Under similar conditions, alkenes yield methoxy bromo compounds [7].

As an alternative to the use of quaternary ammonium tribromide, *N*-bromosuccinimide:tetra-*n*-butylammonium bromide converts alkenes into the dibromoalkanes generally in high yield (>90%) [8]. It is probable that the ammonium tribromide is formed *in situ*.

2.3.6 Dibromoalkanes from alkenes (Table 2.12)

Method A: TBA-Br₃ (3.1 g, 6.4 mmol) is added portionwise with stirring to the alkene (6.4 mmol) in CHCl₃ (25 ml) over a period of *ca.* 20 min. The solution is stirred at room temperature until the red colour has faded to a pale-yellow colour. The solution is then washed with aqueous Na₂SO₃ (5%, 2 × 15 ml) and H₂O (15 ml), dried (Na₂SO₄), and evaporated to yield the dibromoalkane.

Method B: The alkene (39 mmol) in MeCN (30 ml) is refluxed for 3 h with the 1 : 1 *N*-bromosuccinimide: TBA-Br complex (10 g, 20 mmol), prepared by refluxing the imide and TBA-Br in MeCN. The mixture is cooled to room temperature and the solvent removed under reduced pressure. The dibromoalkane is purified by chromatography from silica.

TABLE 2.12
Selected examples of vicinal dibromoalkanes

Alkene	Reaction conditions	% yield
$\text{PhCH}=\text{CH}_2$	2.3.6/10 min	93
$\text{Ph}_2\text{C}=\text{CH}_2$	2.3.6/15 min	85
$E\text{-PhCH}=\text{CHPh}$	2.3.6/15 min	90 ^a
$\text{PhCH}=\text{CHCO}_2\text{H}$	2.3.6/15 min	82 ^b
$\text{PhCH}=\text{CHCOPh}$	2.3.6/4 h	92 ^b
$E\text{-EtO}_2\text{CCH}=\text{CHCO}_2\text{Et}$	2.3.6/15 min	94 ^a

^a meso compound. ^b erythro compound.

2.3.7 Bromination of alkynes

Method A: TBA-Br₃ (1.93 g, 4 mmol) is added portionwise with gentle stirring to the alkyne (4 mmol) in CHCl_3 (18 ml) over a period of 20 min. The solution is stirred at room temperature until the red colour has faded to a pale-yellow colour. The solution is then washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (5%, 20 ml) and H_2O (3×20 ml), dried (Na_2SO_4), and evaporated to yield the *E*-1,2-dibromoalkene (Table 2.13).

Method B: TBA-Br₃ (0.96 g, 2 mmol) is added to the alkyne (2 mmol) in MeOH (100 ml) and the mixture is stirred until the reaction is complete, as shown by TLC analysis. The solvent is removed under reduced pressure and the residue is taken up in Et_2O (50 ml). The ethereal solution is washed well with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (5%) and H_2O , dried (MgSO_4), and evaporated. The dibromoalkenes and dibromodimethoxyalkanes are separated by chromatography (Table 2.14).

TABLE 2.13
Selected examples of *E*-1,2-dibromoalkenes

Alkyne	Reaction conditions	% yield
$\text{PhC}\equiv\text{CH}$	2.3.7.A/48 h	86
$\text{PhC}\equiv\text{CMe}$	2.3.7.A/48 h	84
$\text{PhC}\equiv\text{CPh}$	2.3.7.A/30 h	97
$\text{PhC}\equiv\text{CCO}_2\text{H}$	2.3.7.A/48 h	92
$\text{PhC}\equiv\text{CCHO}$	2.3.7.A/30 h	86
$\text{PhC}\equiv\text{CCH}(\text{OEt})_2$	2.3.7.A/30 h	95
$\text{Me}_2\text{C}(\text{OH})\text{C}\equiv\text{CH}$	2.3.7.A/25 h	88

TABLE 2.14
Selected examples of the bromination of alkynes in methanol

$\text{R}^1\text{C}\equiv\text{CR}^2$	Reaction conditions ^a	% yield	
		$\text{R}^1\text{CBr}=\text{CBrR}^2$	$\text{R}^1\text{C}(\text{OMe})_2\text{CHBr}_2\text{R}^2$
$\text{BuC}\equiv\text{CH}$	2.3.7.B/8 h	20	76
$\text{MeC}\equiv\text{CMe}$	2.3.7.B/5 h	28	65
$\text{PhC}\equiv\text{CH}$	2.3.7.B/20 h	30	65
$\text{PhC}\equiv\text{CPh}$	2.3.7.B/28 h	40	50
$\text{MeOCOC}\equiv\text{CCO}_2\text{Me}$	2.3.7.B/35 h	29	62

^a reaction times can be reduced by a $10\times$ factor under sonication.

2.3.8 1-Bromoalkynes from terminal alkynes

TBA- HSO_4 (2.0 g, 3 mmol) in PhH (5 ml) is added to a vigorously stirred solution of NaBr (1.03 g) in aqueous NaOCl (ca. 6%, 8 ml). The alkyne (3 mmol) in PhH (5 ml) is added and the mixture is stirred at room temperature. On completion of the reaction, as shown by TLC analysis, the organic phase is separated, washed well with brine, aqueous NaHSO_3 (5%) and aqueous NaHCO_3 (5%), dried (MgSO_4), and evaporated to yield the bromoalkyne (e.g. $n\text{-C}_3\text{H}_{11}\text{C}\equiv\text{CBr}$, 70%, $n\text{-C}_6\text{H}_{13}\text{C}\equiv\text{CBr}$, 75%; $\text{PhC}\equiv\text{CBr}$, 82%).

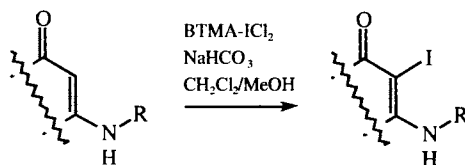
In an analogous manner to the bromination reactions (2.3.6), dichloroalkanes are obtained from alkenes in moderate yields (~50%), when tetra-*n*-butylammonium tetrachloroiodate is used in stoichiometric quantities [9]. The reaction is normally conducted in the dark (Table 2.15).

TABLE 2.15
Selected examples of dichlorination of alkenes and
alkynes using TBA- ICl_4 in the dark

Alkene	Reaction time	% yield
$\text{PhCH}=\text{CH}_2$	4 days	74
<i>E</i> - $\text{PhCH}=\text{CHPh}$	3 days	50 ^a
<i>Z</i> - $\text{PhCH}=\text{CHPh}$	3 days	50 ^b
$\text{PhC}\equiv\text{CPh}$	5 days	47 ^c
cyclo- C_6H_{10}	3 days	48

^a meso compound. ^b DL compound. ^c *trans*- $\text{PhCCl}=\text{CClPh}$.

Quaternary ammonium dichloroiodates [10] are considerably more convenient to use than iodine monochloride for electrophilic iodination reactions and their use in stoichiometric amounts is well documented (see e.g. [11] and references cited therein). Thus, for example, alkenes undergo addition reactions to yield the α -chloro- β -iodoalkanes [11] and enaminones are converted into the corresponding α -iodoenaminones (75–90%) (Scheme 2.4) [12].



Scheme 2.4

2.3.9 Addition of ICl to alkenes

TMBA- ICl_2 (0.92 g, 2.64 mmol) is added with stirring at room temperature to the alkene (2.4 mmol) in CH_2Cl_2 (20 ml) and the solution is stirred until the orange colour has faded

(ca. 2 h). CH_2Cl_2 (20 ml) is added to the reaction mixture, which is then washed with aqueous Na_2SO_3 (5%, 20 ml) and H_2O (20 ml). The dried (MgSO_4) organic solution is evaporated to yield the chloriodoalkane (e.g. *n*- $\text{C}_6\text{H}_{13}\text{CHClCH}_2\text{I}$, 82%; $\text{PhCHClCH}_2\text{I}$ 75%; *trans*-1-chloro-2-iodocyclohexene 83%). Use of a mixed CH_2Cl_2 :MeOH solvent system results in the formation of methoxyiodoalkanes.

2.3.10 α -Iodination of enamminones

TMBA- ICl_2 (0.81 g, 2.3 mmol) is added to the enamminone (2.3 mmol) in CH_2Cl_2 (35 ml) and MeOH (25 ml). NaHCO_3 (1.3 g) is added and the mixture is stirred at room temperature until the orange colour disappears (10–40 min). The mixture is filtered and the filtrate is washed well with aqueous NaHCO_3 (sat. soln) and extracted with CHCl_3 (3×25 ml). The combined organic solutions are washed well with water and brine, dried (Na_2SO_4), and evaporated to yield the α -iodoenaminone.

Alkenes have been converted into dichloro- and dibromoalkanes using the halogen acids under oxidizing conditions [13]. Yields are usually >70% for the dichloro derivatives and >90% for the dibromo compounds. Tetra-*n*-butylammonium hydrogen difluoride and dihydrogen trifluoride react with alkenes in the presence of *N*-chloro- or *N*-bromosuccinimide to produce chloro- or bromofluoroalkanes, respectively, in good yield [14,15], although the products can be contaminated with dichloro and dibromo derivatives. Similarly, the ammonium dihydrogen trifluorides produce fluoroiodoalkanes in the presence of *N*-iodosuccinimide [16]. In the absence of the *N*-halosuccinimides the ammonium salt promotes the addition of HF across the unsaturated system [17]. Tetra-*n*-butylammonium dihydrogen trifluoride and the polymer-bound salt also react with electron-deficient alkynes to produce *Z*- and *E*-fluoroalkenes in ratios of of ca. 4 : 1 and overall yields of 60–85% [18].

2.3.11 Halogenation of alkenes under oxidizing conditions

H_2O_2 (30%, 6 ml) is added with stirring to the alkene (50 mmol) and TEBA-Cl (0.1 g, 0.44 mmol) in CCl_4 (10 ml) and CaCl_2 or CaBr_2 (50 mmol) in conc. HCl or HBr (10 ml) at 0°C. The mixture is allowed to come to room temperature and is stirred for a further 20 min. Petroleum ether (50 ml) is added and the mixture is washed well with H_2O . The dried (Na_2SO_4) organic phase is evaporated to yield the dihaloalkane.

2.3.12 Bromofluorination and chlorofluorination of alkenes

The alkene (2.05 mmol) in CH_2Cl_2 (1 ml) is added to TBA- HF_2 (1.7 g, 6.1 mmol) in CH_2Cl_2 (5 ml), followed by *N*-chloro- or *N*-bromosuccinimide (4.5 mmol). The mixture is stirred at room temperature until the reaction is complete, as shown by GLC analysis. H_2O (20 ml) and CH_2Cl_2 (20 ml) are added and the organic phase is separated, washed well with brine, dried (MgSO_4), and evaporated to yield the halofluoroalkane.

2.3.13 Fluoroiodination of alkenes

TBA- H_2F_3 (0.45 g, 1.5 mmol) and *N*-iodosuccinimide (0.34 g, 1.5 mmol) in CH_2Cl_2 (1.5 ml) are added to the alkene (1 mmol) at 0°C and the mixture is stirred until the

reaction is complete, as shown by GLC analysis. The fluoroiodoalkanes were isolated in the manner analogous to that described in **2.3.12**. [e.g. $\text{PhCH}_2\text{CHFCH}_2\text{I}$ (2 h), 83%; $\text{PhCHFCH}_2\text{I}$ (5 h) 85%; $\text{PhC(Me)FCH}_2\text{I}$ (1 h), 92%; $\text{Me}_2\text{CFCIME}_2$ (1 h), 76%; $\text{Ph}_2\text{CFCH}_2\text{I}$ (2 h), 67%].

2.3.14 Hydrofluorination of alkynes

The alkyne (15 mmol) is added to $\text{TBA-H}_2\text{F}_3$ (9 g, 30 mmol) in $\text{Cl}(\text{CH}_2)_2\text{Cl}$ (1 ml) and the mixture is protected from atmospheric moisture and heated until the reaction is complete. H_2O (5 ml) is added and the mixture is extracted with Et_2O (3×10 ml). The extracts are washed with H_2O to pH 5, dried (Na_2SO_4), and evaporated to yield the *Z*- and *E*-fluoroalkenes [e.g. $\text{MeOCOCF=CHCO}_2\text{Me}$ (60°C, 30 h), 80%; $\text{PhCF=CHCO}_2\text{Me}$ (120°C, 24 h) 85%; PhCF=CHCN (110°C, 20 h), 88%; PhCF=CHCHO (110°C, 4 h), 62%].

Terminal alkynes are converted in high yield (70–80%) into 1-iodoalkynes by their copper-catalysed reaction with iodine under phase-transfer catalytic conditions [19].

2.3.15 1-Iodoalkynes

I_2 (7.6 g, 30 mmol) in DMF (20 ml) is added over 3–4 h to a stirred suspension of K_2CO_3 (8.3 g), CuI (0.29 g), TBA-Cl (1.67 g, 6 mmol), and the alkyne (30 mmol) in DMF (15 ml). Stirring is continued for *ca.* 2 h after the iodine colour has faded. Et_2O (50 ml) is added and the mixture is filtered through Celite. H_2O (100 ml) is added to the filtrate and the mixture is extracted with Et_2O (4×35 ml). The ethereal extracts are washed well with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (0.05 M) and brine, dried (MgSO_4), and evaporated to yield the iodoalkyne, which is purified by chromatography from silica (e.g. $\text{C}_5\text{H}_{11}\text{C}\equiv\text{CI}$, 70%; $\text{PhC}\equiv\text{CI}$, 80%, $\text{IC}\equiv\text{CCO}_2\text{Et}$, 80%).

Chlorination of enolizable ketones can be effected using tetra-*n*-butylammonium tetrachloroiodate [9] and, reportedly, also by benzyltrimethylammonium dichloroiodate [20,21] and by polymer-supported quaternary ammonium dichloroiodates [22]. Similarly, the corresponding reaction with tetra-*n*-butylammonium tribromide yields, almost exclusively, the α -monobromoketones [2] even when a twofold excess of the polyhalide is used [23]. In contrast, reaction with benzyltrimethylammonium tribromide can lead to either the α -monobromo- or α,α -dibromoketone, depending on the amount of tribromide added [24]. This suggests that the benzyltrimethylammonium salt is a more effective brominating agent, but it is not immediately obvious why this is so. Methanol is present in most reactions and it has been suggested that the intermediate reactive species is methyl hypochlorite. In the absence of methanol, benzyltrimethylammonium tetrachloroiodate reacts with acetophenones to produce the dichloroacetyl derivatives [25].

When bromination of the enolizable ketone is conducted in glycol, simultaneous monobromination and acetalization is observed [2]. 1,5-Dicarbonyl compounds react with benzyltrimethylammonium dichloroiodate to yield initially a monochloro derivative, which undergoes ring closure to produce a 2-substituted 5-acylfuran [26].

In all of the halogenation reactions, it is noteworthy that no substitution of the aromatic ring occurs with aryl ketones, even in the case of π -electron-excessive pyrroles [21] or thiophenes [20,23].

2.3.16 Chlorination of enolizable ketones

Method A (monochlorination): TMBA- ICl_2 (3.04 g, 8.73 mmol) is added to the ketone (4.16 mmol) in $\text{Cl}(\text{CH}_2)_2\text{Cl}$ (50 ml) and MeOH (20 ml) and the mixture is refluxed for 3 h. The solvents are evaporated and the residue is washed with aqueous NaHSO_3 (5%, 20 ml) and extracted with Et_2O (4×40 ml). The dried (Na_2SO_4) extracts are evaporated to yield the α -chloroketone (Table 2.16).

Method B (monochlorination): TMBA- ICl_2 (7.0 g, 20 mmol) in THF (25 ml) is added to the ketone (10 mmol) in THF (25 ml) and the mixture is stirred at room temperature for 12–16 h. The THF is evaporated and the residue is taken up in Et_2O (25 ml). The ethereal mixture is washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (5%, 40 ml), dried (Na_2SO_4), and evaporated to yield the α -chloroketone (Table 2.16).

Method C (dichlorination): TMBA- ICl_4 (4.18 g, 10 mmol) is stirred with the acetophenone (5 mmol) in AcOH (50 ml) at 70°C for 5 h. BTMA- ICl_2 is collected by filtration from the cooled mixture and aqueous NaHSO_3 (5%, 10 ml) and NaHCO_3 (5%, 80 ml) are added to the concentrated filtrate. The aqueous mixture is extracted with Et_2O (4×40 ml) and the dried (MgSO_4) extracts are evaporated to yield the dichloroacetyl derivative (Table 2.17).

Method D: Me_3SiCl (1.3 g, 12 mmol) is added dropwise at room temperature to TBA-Br (0.13 g, 0.4 mmol) in MeCN (6 ml), or THF (8 ml). The mixture is stirred for 10 min and the ketone (4 mmol) and DMSO (0.94 g, 12 mmol) are then added with cooling. The mixture is stirred until the reaction is complete and is then poured into H_2O (50 ml),

TABLE 2.16

Selected examples of the mono- α -chlorination of methyl ketones

RCOMe	Reaction conditions	% yield
R = Ph	2.3.16.A/3 h	97 ^a
4-MeC ₆ H ₄	2.3.16.A/3 h	99
4-MeOC ₆ H ₄	2.3.16.A/5 h	97
4-HOC ₆ H ₄	2.3.16.A/10 h	95
4-ClC ₆ H ₄	2.3.16.A/6 h	97
4-MeC ₆ H ₄	2.3.16.A/3 h	99
2-Naphthyl	2.3.16.A/5 h	99
MeCOCH ₂	2.3.16.D/15 min	77 ^b
PhCOCH ₂	2.3.16.D/20 min	93 ^c
2-Thienyl	2.3.16.A/3 h	95
2-Pyrrolyl	2.3.16.B/12 h	85
1-Methyl-2-pyrrolyl	2.3.16.B/12 h	95
1-Benzyl-2-pyrrolyl	2.3.16.B/12 h	82
1-Phenyl-2-pyrrolyl	2.3.16.B/12 h	78
1-Methyl-3-pyrrolyl	2.3.16.B/12 h	75
1-Benzyl-3-pyrrolyl	2.3.16.B/12 h	76
1-Phenyl-3-pyrrolyl	2.3.16.B/12 h	93

^a 62% using 2.3.16. D. ^b MeCOCHClCOMe. ^c PhCOCHClCOMe.

TABLE 2.17
Selected examples of the di- α -chlorination of acetophenones

ArCOMe	Reaction conditions	% yield
Ar = Ph	2.3.16.C/5 h	90
4-MeC ₆ H ₄	2.3.16.C/5 h	91
4-MeOC ₆ H ₄	2.3.16.C/3 h	78
4-ClC ₆ H ₄	2.3.16.C/6 h	79
4-BrC ₆ H ₄	2.3.16.C/6 h	90
4-O ₂ NC ₆ H ₄	2.3.16.C/3 h	90
4-MeCOC ₆ H ₄	2.3.16.C/3 h	77 ^a

^a bis(dichloroacetyl) derivative.

which is extracted with Et₂O (3 \times 8 ml). The ethereal extracts are dried (Na₂SO₄) and evaporated to yield the α -chloroketone.

2.3.17 Bromination of enolizable ketones

Method A. Monobromination: TBA-Br₃ or TMBA-Br₃ (4.58 mmol) is added to the ketone (4.16 mmol) in CH₂Cl₂ (50 ml) and MeOH (20 ml) and the mixture is stirred until it becomes colourless (*ca.* 1 h). The solvent is removed under vacuum and the residue is extracted with Et₂O (4 \times 30 ml). The dried (MgSO₄) ethereal solution is evaporated to yield the monobrominated product (Table 2.18).

Method B. Dibromination: Using TMBA-Br₃ (3.4 g, 8.74 mmol) and the same procedure as described for monobromination yields the α,α -dibromoketones. Use of TBA-Br₃ (4.2 g, 8.74 mmol) results in the formation of a *ca.* 2.5 : 1 ratio of mono and dibromo derivatives) (Table 2.18).

TABLE 2.18
Selected examples of the bromination of enolizable ketones R¹COCH₂R²

R ¹	R ²	Reaction conditions	Product	% yield
<i>t</i> -Bu	Me	2.3.17.A/3 h	R ¹ COCHBrR ²	90
		2.3.17.B/7 h	R ¹ COCBr ₂ R ²	75
Ph	Me	2.3.17.A/1 h	R ¹ COCHBrR ²	86
		2.3.17.B/2 h	R ¹ COCBr ₂ R ²	78
Ph	Et	2.3.17.A/1 h	R ¹ COCHBrR ²	99
Ph	Ph	2.3.17.A/1 h	R ¹ COCHBrR ²	88
4-MeC ₆ H ₄	Me	2.3.17.A/1 h	R ¹ COCHBrR ²	83
		2.3.17.B/2 h	R ¹ COCBr ₂ R ²	88
4-MeOC ₆ H ₄	Me	2.3.17.A/1 h	R ¹ COCHBrR ²	79
		2.3.17.B/2 h	R ¹ COCBr ₂ R ²	87
4-ClC ₆ H ₄	Me	2.3.17.A/3 h	R ¹ COCHBrR ²	85
		2.3.17.B/7 h	R ¹ COCBr ₂ R ²	89
4-BrC ₆ H ₄	Me	2.3.17.A/3 h	R ¹ COCHBrR ²	86
		2.3.17.B/7 h	R ¹ COCBr ₂ R ²	82
4-O ₂ NC ₆ H ₄	Me	2.3.17.A/5 h	R ¹ COCHBrR ²	75
		2.3.17.B/7 h	R ¹ COCBr ₂ R ²	83
2-Furyl	Me	2.3.17.A/2 h	R ¹ COCHBrR ²	85
2-Thienyl	Me	2.3.17.A/2 h	R ¹ COCHBrR ²	80

2.3.18 Bromoacetalization of enolizable ketones

The ketone (0.1 mol) in $(\text{CH}_3\text{OH})_2$ (120 ml) is stirred with TBA- Br_3 (48.2 g, 0.1 mol) at room temperature until the red colour has faded (6–8 h). The bromoacetal is isolated by a procedure analogous to that described in 2.3.6 [e.g. 80% from PhCOMe (6 h); 74% from cyclopentanone (8 h); 78% from cyclohexanone (8 h)].

Tosylhydrazones react with phenyltrimethylammonium tribromide under phase-transfer catalysed basic conditions to yield, initially, α -bromo- and derivatives which, under the basic conditions, eliminate one equivalent of HBr to yield unstable 2-tosylazopropenes [27].

2.3.19 2-Tosylazopropenes

PhTMA- Br_3 (3.76 g, 10 mmol) is added with stirring at room temperature to the tosyl hydrazone (10 mmol), derived from the substituted propanone, in THF (100 ml). When the orange colour has disappeared, Et_2O (50 ml) is added and the mixture is shaken with aqueous Na_2CO_3 (sat. soln., 50 ml). The organic phase is separated, dried (Na_2SO_4), and evaporated under reduced pressure at $<40^\circ\text{C}$ to yield the 2-tosylazopropene [e.g. $\text{PhCH}=\text{C}(\text{Ph})\text{N}=\text{NTos}$, 65%; $\text{PhCH}=\text{C}(\text{CH}_2\text{Ph})\text{N}=\text{NTos}$, 60%; $\text{Ph}_2\text{C}=\text{CHN}=\text{NTos}$, 72%, $(\text{CH}_2)_3\text{C}=\text{CHN}=\text{NTos}$, 64%].

The reaction of enolizable ketones under basic conditions in the presence of carbon tetrachloride, as the source of the chloronium ion, leads to chloroalkanes via the haloform reaction, or oxiranes [28, 29]. For example, 1-phenylpropan-2-one is converted into 2-methyl-2-trichloromethyl-3-phenyloxirane (12.7%), benzalchloride (30%) and benzotrichloride (7.5%) [28, 29]. Although of some mechanistic interest, the procedure has little synthetic value. In contrast, α -chlorination of enolizable ketones in high yield can be attained by their reaction with a combination of tetra-*n*-butylammonium bromide, dimethylsulphoxide and trimethylsilyl chloride (2.3.16.D) [30]. In the absence of the ammonium salt, no reaction occurs. Glycols react with quaternary ammonium tribromides stereoselectively to yield 2-bromo-2-deoxyglycopyranosyl bromides with predominantly the α -1,2-*trans* configuration [30]. Optimum yields and stereoselectivity ($>90\%$) are attained using solvents with high dielectric constants. With solvents of low dielectric constant, higher yields of the other isomers are obtained, together with the 2-bromoglycals.

2.3.20 2-Bromo-2-deoxyglycopyranosyl bromides

TBA- Br_3 , or TMBA- Br_3 (1 mmol) is added to the glycol (1 mmol) in a suitable solvent, e.g. MeCN, THF or EtOAc (5 ml) and the mixture is stirred at room temperature for ca. 2 h. The yellow solution is filtered, evaporated, and the residue is taken up in CHCl_3 . Evaporation of the organic solution yields, mainly, the α -1,2-*trans*-2-bromo-2-deoxyglycopyranosyl bromide.

As with the standard halogenation of inactivated and weakly activated arenes, a

Lewis acid catalyst is normally required when ammonium polyhalides are used, although recourse does not have to be made to strong acids, such as aluminium trichloride. Bromination and iodination reactions are normally conducted in acetic acid in the presence of zinc chloride [32], but chlorination using the ammonium tetrachloroiodate in acetic acid does not require the additional presence of a Lewis acid [33]. Radical chlorination of toluenes by benzyltrimethylammonium tetrachloroiodate in the presence of AIBN gives mixtures of the mono- and dichloromethylbenzenes [34]. Photo-catalysed side-chain chlorination is less successful [35]. Radical bromination using the tribromide with AIBN or benzoyl peroxide has also been reported [36, 37].

As an alternative to radical chlorination, use has been made of carbon tetrachloride and hexachloroethane in the presence of a quaternary ammonium salt, as source of the chloronium ion for reaction with activated alkylbenzenes [38]. Benzyl chlorides need the additional activation of a nitro group for their conversion into the corresponding nitrobenzotrichlorides, whereas benzal chlorides do not need the extra activation for a similar conversion. The same synthetic protocol, using hexachloroethane, has been used for the conversion of allylic sulphones into the 1,1-dichloro derivatives [39].

2.3.21 Chlorination of inactivated arenes

TMBA- ICl_4 (1.74 g, 4.16 mmol) is added to the arene (4.16 mmol) in AcOH (30 ml) and the mixture is stirred for 20–48 h at 70°C. The precipitated TMBA- ICl_2 is collected and the filtrate is washed with aqueous NaHSO_3 (5%, 20 ml) and extracted with $n\text{-C}_6\text{H}_{14}$ (4 × 25 ml). The extracts are washed with aqueous NaHCO_3 (5%, 30 ml), dried (MgSO_4), and evaporated to yield the monochloroarene (Table 2.19).

2.3.22 Bromination of inactivated arenes

TMBA- Br_3 (1.84 g, 4.71 g) and ZnCl_2 (0.7 g) are added to the arene (4.71 mmol) in AcOH (30 ml) and the mixture is stirred until the colour fades. H_2O (20 ml) and aqueous NaHCO_3 (5%, 10 ml) are added and the mixture is extracted with $n\text{-C}_6\text{H}_{14}$ (4 × 40 ml). The extracts are dried (MgSO_4) and evaporated to yield the monobromoarene, which can be purified by chromatography from alumina (Table 2.19).

2.3.23 Iodination of inactivated arenes

Using the procedure outlined in 2.3.22, but replacing TMBA- Br_3 with TMBA- ICl_2 (1.64 g, 4.71 mmol), gives the moniodoarene (Table 2.19).

2.3.24 Radical halogenation of alkylbenzenes (Table 2.20)

Method A. Chlorination: TMBA- ICl_4 (22.7 g, 54 mmol) is added to the alkylbenzene (54 mmol) and AIBN (0.89 g, 5.4 mmol) in CCl_4 (300 ml) and the solution is refluxed. Precipitated TMBA- ICl_2 is removed from the cooled solution and the filtrate is concentrated. $n\text{-C}_6\text{H}_{14}$ (30 ml) is added to the concentrate and the chlorinated products isolated by chromatography from silica.

TABLE 2.19
Selected examples of the halogenation of inactivated arenes

Arene	Reaction conditions	Product	% yield
PhH	2.3.21/48 h	C ₆ H ₅ Cl	16
PhMe	2.3.21/24 h	2-ClC ₆ H ₄ Me	62
		4-ClC ₆ H ₄ Me	26
1,2-Me ₂ C ₆ H ₄	2.3.21/20 h	4-Cl-1,2-Me ₂ C ₆ H ₃	70
1,2-Me ₂ C ₆ H ₄	2.3.22/2 h	4-Br-1,2-Me ₂ C ₆ H ₃	69
1,2-Me ₂ C ₆ H ₄	2.3.23/24 h	4-I-1,2-Me ₂ C ₆ H ₃	40
1,3-Me ₂ C ₆ H ₄	2.3.21/20 h	4-Cl-1,3-Me ₂ C ₆ H ₃	60
		6-Cl-1,3-Me ₂ C ₆ H ₃	30
1,3-Me ₂ C ₆ H ₄	2.3.22/1 h	4-Br-1,3-Me ₂ C ₆ H ₃	73
1,3-Me ₂ C ₆ H ₄	2.3.23/24 h	4-I-1,3-Me ₂ C ₆ H ₃	66
1,4-Me ₂ C ₆ H ₄	2.3.21/20 h	2-Cl-1,4-Me ₂ C ₆ H ₃	60
1,4-Me ₂ C ₆ H ₄	2.3.22/2 h	2-Br-1,4-Me ₂ C ₆ H ₃	84
1,4-Me ₂ C ₆ H ₄	2.3.23/16 h	2-I-1,4-Me ₂ C ₆ H ₃	75
Naphthalene	2.3.21/24 h	1-ClC ₁₀ H ₇	65
1-Methylnaphthalene	2.3.21/24 h	4-Cl-1-MeC ₁₀ H ₆	73
2-Methylnaphthalene	2.3.21/24 h	1-Cl-2-MeC ₁₀ H ₆	95

TABLE 2.20
Selected examples of the radical halogenation of alkylbenzenes

Alkylbenzene	Reaction conditions	Products
PhMe	2.3.24.A/4 h	PhCH ₂ Cl (77%); PhCHCl ₂ (11%)
	2.3.24.B/15 min	PhCH ₂ Br (59%)
PhEt	2.3.24.A/5 h	PhCHClMe (53%); PhCH ₂ CH ₂ Cl (18%); PhCHClCH ₂ Cl (9%); PhCCl ₂ Me (5%)
Ph ₂ CH ₂	2.3.24.A/4 h	Ph ₂ CHCl (86%)
Ph ₃ CH	2.3.24.A/1 h	Ph ₃ CCl (99%)
1,2-MeC ₆ H ₄	2.3.24.A/6 h	2-ClCH ₂ C ₆ H ₄ Me (30%); 1,2-(ClCH ₂) ₂ C ₆ H ₄ (49%); 1-(ClCH ₂)C ₆ H ₄ -2-CHCl ₂ (12%)
1-MeC ₁₀ H ₇	2.3.4.B/24 h	1-BrCH ₂ C ₁₀ H ₇ (57%)
2-MeC ₁₀ H ₇	2.3.4.B/8 h	2-BrCH ₂ C ₁₀ H ₇ (62%)

Method B. Bromination: TMA-Br₃ (1.54 g, 10 mmol) and (PhCO)₂O₂ (0.24 g, 1 mmol) is added to the alkylarene (10 mmol) in PhH (20 ml) at room temperature and the mixture is stirred until the colour disappears and the evolution of HBr stops. H₂O (20 ml) is added and the organic phase is separated, washed well with H₂O and aqueous Na₂CO₃ (sat. soln.), dried (Na₂SO₄), and evaporated to yield the brominated product.

2.3.25 Benzotrichlorides (Table 2.21)

Method A: The appropriate benzyl chloride or benzal dichloride (50 mmol) and DDTMA-Cl (0.6 g, 2.1 mmol) in CH₂Cl₂ (160 ml) are stirred with CCl₄ (100 ml) and

TABLE 2.21
 Benzotrichlorides

Substrate	Method	Yield %
2-O ₂ NC ₆ H ₄ CH ₂ Cl	2.3.25.A	70
3-Me-2-O ₂ NC ₆ H ₄ CH ₂ Cl	2.3.25.A	84
2-MeC ₆ H ₄ CHCl ₂	2.3.25.B	33
3-MeC ₆ H ₄ CHCl ₂	2.3.25.B	87
4-MeC ₆ H ₄ CHCl ₂	2.3.25.B	71
2-ClC ₆ H ₄ CHCl ₂	2.3.25.B	91

aqueous NaOH (50%, 250 ml) and *t*-BuOH (10 g) and the mixture is refluxed for *ca.* 3.5 h. Ice/H₂O (50 g) and CH₂Cl₂ (25 ml) are added to the cooled mixture, the organic phase is separated, dried (MgSO₄), and fractionally distilled to yield the benzotrichloride. *Method B:* Aqueous NaOH (50%, 60 ml) and DDTMA-Cl (0.7 g, 2.4 mmol) in Cl₂C=CCl₂ (140 ml) are added to the benzal dichloride (0.2 mol) and C₂Cl₆ (54 g, 0.23 mol), and the mixture is stirred under reflux with azeotropic distillation of water for *ca.* 1 h. The organic phase is separated from the cooled mixture and fractionally distilled to yield the benzotrichloride.

Bromobenzenes are converted into the corresponding chloro compounds on reaction with aqueous sodium hypochlorite in the presence of tetra-*n*-butylammonium hydrogen sulphate [40]. The reaction is pH dependent. At pH > 10, the bromobenzenes are effectively inert, but over the pH range 7.5–9, conversion occurs into the chlorobenzenes without any side reactions and the reaction appears to be light-induced. At more acidic levels (pH 4–5), bromobenzene is converted quantitatively into chlorobenzene within one hour. No reaction occurs in the absence of the catalyst and yields from 'light' and 'dark' reactions are comparable. Side reactions are observed, however, with substituted bromobenzenes under these low pH conditions.

π -Electron excessive aromatic rings are readily halogenated under mild conditions on reaction with a stoichiometric amount of a quaternary ammonium polyhalide. It was initially demonstrated that aniline [41] and phenol [42] are specifically monobrominated in the 4-position by tetra-*n*-butylammonium tribromide at room temperature in under 3 minutes. When the 4-position is blocked, monobromination occurs at a vacant 2-position. Under similar conditions, acetanilides, phenyl ethers, and phenyl alkanoates do not react even after 15 hours and iodination of acetanilides has been shown to require the presence of zinc chloride [43]. Reaction with more than one equivalent of the polyhalide in a dichloromethane/methanol mixture was later shown to lead to polyhaloanilines, even when the ring was substituted by electron-withdrawing groups [e.g. 44, 45]. It has been suggested that in this procedure the reactive species is methyl hypohalite and, under these conditions, polyhalogenation of phenols has also been reported [e.g. 10, 46]; acetanilides [47] and aryl ethers [48] are also brominated. It is also evident that benzytrimethylammonium dibromochlorate is a better brominating agent than tetra-*n*-butylammonium or benzytrimethylammonium

tribromide [47]. Chlorination of aryl ethers in acetic acid using the tetrachloroiodate salt fails when the aryl ring is substituted by strongly electron-withdrawing substituents [49], and iodination reactions require the addition of zinc chloride [50].

Acetanilides and phenyl ethers having strongly electron-withdrawing substituents do not react easily under these conditions and need the additional catalytic influence of zinc chloride or acetic acid [51].

Although chlorination, bromination and iodination of thiophenes by polyhalide salts require forcing conditions with the addition of zinc chloride [52], halogenation of acridine and acridone has been recorded to yield both 3-halo and 3,7-dihalo derivatives under relatively mild reaction conditions [53]. However, whereas chloro-, bromo- and iodo-compounds are readily obtained from acridone, acridine only forms the bromo derivatives, as it produces stable complexes with the dichloroiodate and tetrachloroiodate salts [53].

2.3.26 Bromination of anilines

Method A: TBA-Br₃ (1 g, 2 mmol) is added to the aniline (2 mmol) in CHCl₃ (15 ml) at 20°C. The solution is stirred until it becomes colourless and is then washed with aqueous Na₂S₂O₃ (sat. soln) and H₂O until the washings are pH 7.0. The organic phase is evaporated and the residue is taken up in Et₂O (20 ml), which is then washed well with H₂O, dried (Na₂SO₄), and evaporated to give the monobromoaniline.

Method B: TMBA-Br₃ (see Table 2.22) and CaCO₃ (2 g) is added to the aniline (5.37 mmol) in CH₂Cl₂ (50 ml) and MeOH (20 ml). The mixture is stirred for 30 min until the orange colour fades, then filtered. The filtrate is concentrated, H₂O (20 ml) is added, and the mixture is extracted with Et₂O (4 × 40 ml). The dried (MgSO₄) extracts are evaporated to yield the brominated aniline.

2.3.27 Bromination of phenols

Method A: TBA-Br₃ (1 g, 2 mmol) is added to the phenol (2 mmol) in CHCl₃ (15 ml) and the solution is stirred at ca. 20°C. When the solution is colourless, it is washed well with aqueous Na₂S₂O₃ (5%) and H₂O until pH 7.0 and the organic phase is evaporated. The residue is taken up in Et₂O (20 ml), washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the monobromophenol.

Method B: TMBA-Br₃ (see Table 2.22) is added to the phenol (4.62 mmol) in CH₂Cl₂ (50 ml) and MeOH (20 ml). The mixture is stirred for 1 h at room temperature until the orange colour fades. The solvent is evaporated and the residue is extracted with Et₂O (4 × 40 ml). The dried (MgSO₄) extracts are evaporated to yield the brominated phenol.

2.3.28 Iodination of anilines

TMBA-ICl₂ (see Table 2.23) is added to the aniline (5.37 mmol) in CH₂Cl₂ (50 ml) and MeOH (20 ml) at room temperature and the mixture is stirred for 30 min and then filtered and concentrated. Aqueous NaHSO₃ (5%, 20 ml) is added to the residue and extracted with Et₂O (4 × 40 ml). The dried (MgSO₄) extracts are evaporated to yield the iodinated aniline.

TABLE 2.22
Selected examples of the bromination of anilines and phenols

Arene	Reaction conditions	Product	% yield
PhNH ₂	2.3.26.A ^a /3 min	4-BrC ₆ H ₄ NH ₂	82
	2.3.26.B ^b /30 min	2,4,6-Br ₃ C ₆ H ₂ NH ₂	93
PhNHMe	2.3.26.A ^a /2 min	4-BrC ₆ H ₄ NHMe	94
PhNEt ₂	2.3.26.A ^a /2 min	4-BrC ₆ H ₄ NEt ₂	99
Ph ₂ NH	2.3.26.A ^a /2 min	(4-BrC ₆ H ₄) ₂ NH	99
	2.3.26.B ^b /30 min	(2,4-Br ₂ C ₆ H ₃) ₂ NH	90
2,6-Me ₂ C ₆ H ₃ NH ₂	2.3.26.B ^b /30 min	4-Br-2,6-Me ₂ C ₆ H ₃ NH ₂	83
4-MeOC ₆ H ₄ NH ₂	2.3.26.B ^b /30 min	2,6-Br ₂ -4-MeOC ₆ H ₃ NH ₂	78
3-EtOC ₆ H ₄ NH ₂	2.3.26.B ^b /30 min	2,4,6-Br ₃ -3-EtOC ₆ H ₃ NH ₂	93
4-Me-2-O ₂ NC ₆ H ₃ NH ₂	2.3.26.B ^b /30 min	6-Br-4-Me-2-O ₂ NC ₆ H ₂ NH ₂	78
2-Me-3-O ₂ NC ₆ H ₃ NH ₂	2.3.26.B ^b /30 min	4,6-Br ₂ -2-Me-3-O ₂ NC ₆ H ₂ NH ₂	78
2-Aminopyridine	2.3.26.A ^a /2 min	2-Amino-5-bromopyridine	98
PhOH	2.3.27.A ^a /2 min	4-BrC ₆ H ₄ OH	95
	2.3.27.B ^{b,c} /1 h	2,4,6-Br ₃ C ₆ H ₂ OH	92
2-MeC ₆ H ₄ OH	2.3.27.A ^a /2 min	4-Br-2-MeC ₆ H ₃ OH	96
4-MeC ₆ H ₄ OH	2.3.27.A ^a /14 min	2-Br-4-MeC ₆ H ₃ OH	93
	2.3.27.B ^b /1 h	2,6-Br ₂ -4-MeC ₆ H ₂ OH	93
2-MeOC ₆ H ₄ OH	2.3.27.B ^b /1 h	4,6-Br ₂ -2-MeOC ₆ H ₃ OH	90
3-MeOC ₆ H ₄ OH	2.3.27.B ^{b,c} /1 h	2,4,6-Br ₃ -3-MeOC ₆ H ₂ OH	92
2-O ₂ NC ₆ H ₄ OH	2.3.27.B ^{b,c} /1 h	4,6-Br ₂ -2-O ₂ NC ₆ H ₃ OH	92
3-O ₂ NC ₆ H ₄ OH	2.3.27.B ^{b,c} /1 h	2,4,6-Br ₃ -3-O ₂ NC ₆ H ₂ OH	90
4-O ₂ NC ₆ H ₄ OH	2.3.27.B ^{b,c} /1 h	2,6-Br ₂ -4-O ₂ NC ₆ H ₃ OH	90
4-HOC ₆ H ₄ OH	2.3.27.B ^{b,c} /1 h	2,5-Br ₂ -4-HOC ₆ H ₃ OH	84
1-Naphthol	2.3.27.A ^a /2 min	4-Bromo-1-naphthol	95
2-Naphthol	2.3.27.A ^a /2 min	1-Bromo-2-naphthol	95

^a 1 mol equiv. TMBA-Br₃, ^b 3 mol equiv. TMBA-Br₃, ^c 2 mol equiv. TMBA-Br₃, ^d 4 mol equiv. TMBA-Br₃, ^e with addition of CaCO₃ (2 g).

2.3.29 Iodination of phenols

TMBA-ICl₂ (see Table 2.23) and NaHCO₃ (3 g) are added to the phenol (5.37 mmol) in CH₂Cl₂ (50 ml) and MeOH (20 ml) at room temperature and the mixture is stirred for 30 min and then filtered and concentrated. Aqueous NaHSO₃ (5%, 20 ml) is added to the residue and extracted with Et₂O (4 × 40 ml). The dried (MgSO₄) extracts are evaporated to yield the iodinated phenol.

2.3.30 Chlorination of acetanilides

TMBA-ICl₄ (1.3 g, 3.1 mmol) is added to the acetanilide (3.1 mmol) in AcOH (30 ml) and the mixture is stirred for 24 h at room temperature. The precipitated TMBA-ICl₂ is collected and the filtrate is evaporated under vacuum. The residue is washed with NaHSO₃ (5%, 10 ml), NaHCO₃ (5%, 15 ml) and extracted with CH₂Cl₂ (3 × 20 ml). The organic extracts are filtered through Al₂O₃ and evaporated to yield the chlorinated acetanilide.

TABLE 2.23
Selected examples of the iodination of anilines and phenols

Arene	Reaction conditions	Product	% yield
PhNH ₂	2.3.28 ^a /30 min	4-IC ₆ H ₄ NH ₂	94
	2.3.28 ^b /2 h	2,4-I ₂ C ₆ H ₃ NH ₂	75
2,6-Me ₂ C ₆ H ₃ NH ₂	2.3.28 ^a /1 h	4-I-2,6-Me ₂ C ₆ H ₂ NH ₂	96
3-EtOC ₆ H ₄ NH ₂	2.3.28 ^b /8 h	4,6-I ₂ -3-EtOC ₆ H ₂ NH ₂	96
4-BrC ₆ H ₄ NH ₂	2.3.28 ^a /8 h	4-Br-2-IC ₆ H ₃ NH ₂	89
PhNHPh	2.3.28 ^b /4 h	(4-IC ₆ H ₄) ₂ NH	96
PhOH	2.3.29 ^c /7 h	2,4,6-I ₃ C ₆ H ₂ OH	72
2-MeC ₆ H ₄ OH	2.3.29 ^b /4 h	4,6-I ₂ -2-MeC ₆ H ₂ OH	70
3,5-Me ₂ C ₆ H ₃ OH	2.3.29 ^a /4 h	4-I-3,5-Me ₂ C ₆ H ₂ OH	67
2-O ₂ NC ₆ H ₄ OH	2.3.29 ^b /7 h	4,6-I ₂ -2-O ₂ NC ₆ H ₂ OH	96
2-O ₂ N-4-MeC ₆ H ₃ OH	2.3.29 ^a /6 h	6-I-2-O ₂ N-4-MeC ₆ H ₂ OH	95

^a 1 mol equiv. TMBA-ICl₂, ^b 2 mol equiv. TMBA-ICl₂, ^c 3 mol equiv. TMBA-ICl₂.

2.3.31 Bromination of acetanilides (Table 2.24)

TMBA-CIBr₂ (1.41 g, 4.08 mmol) is added to the acetanilides (3.7 mmol) in CH₂Cl₂ (50 ml) and MeOH (20 ml) and the mixture is stirred at room temperature until the solution is colourless (*ca.* 20 min). The solvent is evaporated and the residue is taken up in H₂O (20 ml), which is extracted with Et₂O (4 × 40 ml). The dried (MgSO₄) extracts are evaporated to yield the bromoacetanilide.

2.3.32 Iodination of acetanilides (Table 2.25)

TMBA-ICl₂ (1.42 g, 4.1 mmol) and ZnCl₂ (0.7 g) are added to the acetanilide (3.7 mmol) in AcOH (20 ml) and the mixture is stirred at room temperature until the colour has faded. The mixture is concentrated under reduced pressure, aqueous NaHSO₃ (5%, 10 ml) is added, and the mixture is neutralized with aqueous NaHCO₃ (5%) and extracted with CH₂Cl₂ (4 × 40 ml). The dried (MgSO₄) extracts are evaporated to yield the iodoacetanilide.

TABLE 2.24
Selected examples of the bromination of acetanilides

ArNHCOMe	Reaction conditions	Product	% yield
Ar = Ph	2.3.31/20 min	4-BrC ₆ H ₄ NHCOMe	97
2-MeC ₆ H ₄	2.3.31/10 h	4-Br-2-MeC ₆ H ₃ NHCOMe	99
3-MeC ₆ H ₄	2.3.31/15 min	4-Br-3-MeC ₆ H ₃ NHCOMe	99
3,5-Me ₂ C ₆ H ₃	2.3.31/1 h	4-Br-3,5-Me ₂ C ₆ H ₂ NHCOMe	96
2-HOC ₆ H ₄	2.3.31/1 h	5-Br-2-HOC ₆ H ₃ NHCOMe	96
	2.3.31 ^a /2 h	3,5-Br ₂ -2-HOC ₆ H ₂ NHCOMe	89
3-HOC ₆ H ₄ N	2.3.31 ^a /2 h	4,6-Br ₂ -3-HOC ₆ H ₂ NHCOMe	88
	2.3.31 ^b /14 h	2,4,6-Br ₃ -3-HOC ₆ HNNHCOMe	93
3-H ₂ NC ₆ H ₄	2.3.31 ^b /3 h	2,4,6-Br ₃ -3-H ₂ NC ₆ HNNHCOMe	98

^a 2 equivalents of TMBA-Br₂, ^b 3 equivalents of TMBA-Br₂.

TABLE 2.25
Selected examples of the iodination of acetanilides

ArNHCOMe	Reaction conditions	Product	% yield
Ar = Ph	2.3.32 /2 h	4-IC ₆ H ₄ NHCOMe	77
2-MeC ₆ H ₄	2.3.32 /4 h	4-I-2-MeC ₆ H ₃ NHCOMe	86
3-MeC ₆ H ₄	2.3.32 /30 min	4-I-3-MeC ₆ H ₃ NHCOMe	97
4-MeC ₆ H ₄	2.3.32 /24 h	2-I-4-MeC ₆ H ₃ NHCOMe	70
4-MeOC ₆ H ₄	2.3.32 /48 h	3-I-4-MeOC ₆ H ₃ NHCOMe	90

2.3.33 Chlorination of aryl ethers (Table 2.26)

TMBA-ICl₄ (19.3 g, 46 mmol) is added portionwise to the aryl ether (46 mmol) in AcOH (100 ml) and the mixture is stirred for 24 h at 70 °C. Over this time the yellow solution becomes reddish brown and TMBA-ICl₂ precipitates. The salt is collected and the filtrate is washed with aqueous NaHSO₃ (5%, 200 ml) and extracted with PhH (3 × 40 ml). The extracts are washed with aqueous NaHCO₃ (5%, 150 ml), dried (MgSO₄), and evaporated to yield the chlorophenyl ether.

2.3.34 Bromination of aryl ethers (Table 2.27)

Method A: TMBA-Br₃ (1.98 g, 5.1 mmol) is added to the aryl ether (4.62 mmol) in CH₂Cl₂ (50 ml) and MeOH (20 ml) and the mixture is stirred at room temperature for *ca.* 2 h. Over this time, the colour of the orange solution fades. The solvent is evaporated under reduced pressure and H₂O (20 ml) is added to the residue, which is then extracted with Et₂O (4 × 40 ml). The dried (MgSO₄) extracts are evaporated to yield the bromophenyl ether.

Method B: TMBA-Br₃ (1.89 g, 4.86 mmol for monobromination; 3.79 g, 9.72 mmol for dibromination) and ZnCl₂ (1.5 g) are added to the aryl ether (4.62 mmol) in AcOH

TABLE 2.26
Selected examples of the chlorination of aryl ethers

Aryl ether	Reaction conditions	Products
PhOMe	2.3.33 /24 h	4-ClC ₆ H ₄ OMe (52%); 2-ClC ₆ H ₄ OMe (21%) ^a
PhOEt	2.3.33 /24 h	4-ClC ₆ H ₄ OEt (72%); 2-ClC ₆ H ₄ OEt (24%)
2-MeC ₆ H ₄ OMe	2.3.33 /20 h	4-Cl-2-MeC ₆ H ₃ OMe (75%)
3-MeC ₆ H ₄ OMe	2.3.33 /20 h	4-Cl-3-MeC ₆ H ₃ OMe (74%)
4-MeC ₆ H ₄ OMe	2.3.33 /20 h	2-Cl-4-MeC ₆ H ₃ OMe (73%)
2-MeOC ₆ H ₄ OMe	2.3.33 /20 h	4-Cl-2-MeOC ₆ H ₃ OMe (73%) ^{b,c}
4-MeOC ₆ H ₄ OMe	2.3.33 /20 h	2-Cl-4-MeOC ₆ H ₃ OMe (65%) ^{b,d}
PhOPh	2.3.33 /24 h	4-ClC ₆ H ₄ OPh (92%) ^e

^a 96% of 2,4-dichloro compound using 2 equiv. of TMBA-ICl₄. ^b in CH₂Cl₂ at room temperature. ^c 94% of 4,5-dichloro compound using 2 equiv. of TMBA-ICl₄ in AcOH over 1 h. ^d 90% of 2,5-dichloro compound using 2 equiv. of TMBA-ICl₄ in AcOH over 1 h. ^e at room temperature.

TABLE 2.27
Selected examples of the bromination of aryl ethers

Aryl ether	Reaction conditions	Product	% yield
PhOMe	2.3.34.A/2 h	4-BrC ₆ H ₄ OMe	98
	2.3.34.B ^a /2 h	2,4-Br ₂ C ₆ H ₃ OMe	97
PhOEt	2.3.34.A/1 h	4-BrC ₆ H ₄ OEt	98
	2.3.34.B ^a /2 h	2,4-Br ₂ C ₆ H ₃ OEt	98
PhOPh	2.3.34.B/20 min	(4-BrC ₆ H ₄) ₂ O	98
2-MeC ₆ H ₄ OMe	2.3.34.A/30 min	4-Br-2-MeC ₆ H ₃ OMe	98
	2.3.34.B ^a /8 h	2,4-Br ₂ -6-MeC ₆ H ₂ OMe	94
3-MeC ₆ H ₄ OMe	2.3.34.A/3 min	4-Br-3-MeC ₆ H ₃ OMe	98
4-MeC ₆ H ₄ OMe	2.3.34.B ^a /10 min	2-Br-4-MeC ₆ H ₃ OMe	93
1,2-(MeO) ₂ C ₆ H ₄	2.3.34.A/1 h	4-Br-1,2-(MeO) ₂ C ₆ H ₃	98
1,4-(MeO) ₂ C ₆ H ₄	2.3.34.B ^a /3 h	2,5-Br ₂ -1,4-(MeO) ₂ C ₆ H ₂	98
4-O ₂ NC ₆ H ₄ OMe	2.3.34.B ^a /17 h	2-Br-4-O ₂ NC ₆ H ₃ OMe	97

^a using 2 equiv. of TMBA-Br₃, ^b using 1 equiv. TMBA-Br₃.

(20 ml) and the mixture is stirred at 70°C for *ca.* 2 h until the orange colour of the solution has faded. H₂O (20 ml) and aqueous Na₂SO₃ (5%, 10 ml) are added and the aqueous mixture is extracted with *n*-C₆H₁₄ (4 × 40 ml). The dried (MgSO₄) extracts are evaporated to yield the bromophenyl ether.

2.3.35 Iodination of aryl ethers (Table 2.28)

TMBA-ICl₂ (1.77 g, 5.1 mmol) and anhydrous ZnCl₂ (1 g) is added to the aryl ether in AcOH (30 ml) and the mixture is stirred at room temperature for *ca.* 3 h. When the yellow solution has turned to reddish brown, H₂O (20 ml) and aqueous NaHSO₃ (5%, 20 ml) are added and the aqueous mixture is extracted with *n*-C₆H₁₄ (3 × 50 ml). The dried (MgSO₄), extracts are evaporated to yield the iodophenyl ether.

2.3.36 Electrophilic halogenation of acridine and acridone

Monohalogenation: Acridine or acridone (2 mmol) and TMBA-X_n (2 mmol; using TMBA-Br₃ for bromination, TMBA-ICl₄ for chlorination, TMBA-ICl₂ for iodination) are

TABLE 2.28
Selected examples of the iodination of aryl ethers

Aryl ether	Reaction conditions	Product	% yield
PhOMe	2.3.35/3 h	4-IC ₆ H ₄ OMe	92
PhOEt	2.3.35/2 h	4-IC ₆ H ₄ OEt	97
PhOCH ₂ Ph	2.3.35/2 h	4-IC ₆ H ₄ OCH ₂ Ph	90
2-MeC ₆ H ₄ OMe	2.3.35/30 min	4-I-2-MeC ₆ H ₃ OMe	97
3-MeC ₆ H ₄ OMe	2.3.35/30 min	4-I-3-MeC ₆ H ₃ OMe	94
4-MeC ₆ H ₄ OMe	2.3.35/6 h	2-I-4-MeC ₆ H ₃ OMe	94
4-MeOC ₆ H ₄ OMe	2.3.35/30 min	4-I-2-MeOC ₆ H ₃ OMe	97

stirred in AcOH (15 ml) and MeOH (5 ml, omitted in reaction with acridone) at room temperature for 8 h (20 h for acridone). The mono-halo derivative precipitates from solution (3-bromoacridine 60%; 3-bromoacridone 60%; 3-chloroacridone 60%; 3-iodoacridone 50–80%).

Dihalogenation: Acridine or acridone (1 mmol) and TMBA-X_n (2 mmol) are stirred in MeOH (20 ml) [AcOH (50 ml) for acridone] at 80°C for 2 h (8 h for acridone). The mixture is cooled to room temperature and the precipitated dihalo derivative is collected (3,7-dibromoacridine 70%; 3,7-dibromoacridone 80%; 3,7-dichloroacridone 65%).

Benzyltrimethylammonium tribromide has been used for the *N*-bromination of amides in good yield [54]. Under basic conditions, Hofmann rearrangement to amines is also possible (see Section 9.3).

2.3.37 *N*-Bromination of amides

TMBA-Br₃ (1.95 g, 5 mmol) is added to aqueous NaOH (0.25 M, 20 ml) over a period of 30 min at 0°C. The amide (5 mmol) is then added and the mixture stirred at 0°C for 4 h. The precipitate is collected, washed well with aqueous AcOH (10%), and dried under vacuum to yield the *N*-bromoamide (e.g. *n*-C₇H₁₅CONHBr, 77%; PhCH₂CONHBr, 63%; PhCONHBr, 53%; 4-ClC₆H₄CONHBr, 86%; 4-O₂NC₆H₄CONHBr, 82%).

Bromomethylation of arenes using 1,3,5-trioxane and hydrobromic acid is catalysed by the addition of a phase-transfer catalyst. Yields in excess of 90% are attained using (tetradecyl)trimethylammonium bromide under relatively mild conditions for a range of arenes [55]. Tetra-*n*-butylammonium bromide is ineffective, suggesting the catalytic effect may be micellar.

2.3.38 Bromomethylation of arenes

The arene (1 mol) is added to aqueous HBr (48%, 475 ml) and AcOH (125 ml), followed by 1,3,5-trioxane (60 g, 2 mol) and TDTMA-Br (5 g, 14.8 mmol). The mixture is stirred at room temperature until only one layer is apparent and then heated under reflux for 10–24 h. The mixture is cooled to 20°C and the precipitate is collected, washed well with H₂O and extracted with hot *n*-C₆H₁₄:CH₂Cl₂ (1 : 1, 3 × 35 ml). The bromomethyl derivative crystallizes from the cooled extracts (e.g. PhCH₂Br, 90%; 4-MeC₆H₄CH₂Br, 96%; 2,4,6-Me₃C₆H₂Br, 96%; 1-naphthylCH₂Br, 95%).

The rate and yield of electrophilic coupling of arenediazonium salts with π -excessive aromatic systems has been found to be enhanced by the addition of tetra-*n*-butylammonium bromide [56].

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– 3 –

Formation of C–O Bonds

3.1 ALKYLATION OF ALCOHOLS AND RELATED COMPOUNDS

The application of phase-transfer catalysis to the Williamson synthesis of ethers has been exploited widely and is far superior to any classical method for the synthesis of aliphatic ethers. Probably the first example of the use of a quaternary ammonium salt to promote a nucleophilic substitution reaction is the formation of a benzyl ether using a stoichiometric amount of tetraethylammonium hydroxide [1]. Starks mentions the potential value of the quaternary ammonium catalyst for Williamson synthesis of ethers [2] and its versatility in the synthesis of methyl ethers and other alkyl ethers was soon established [3–5]. The procedure has considerable advantages over the classical Williamson synthesis both in reaction time and yields and is certainly more convenient than the use of diazomethane for the preparation of methyl ethers. Under liquid:liquid two-phase conditions, tertiary and secondary alcohols react less readily than do primary alcohols, and secondary alkyl halides tend to be ineffective. However, reactions which one might expect to be sterically inhibited are successful under phase-transfer catalytic conditions [e.g. 6]. Microwave irradiation and solid:liquid phase-transfer catalytic conditions reduce reaction times considerably [7].

As the integrity of chiral alcohols are retained in the phase-transfer catalysed *O*-alkylation, the procedure is valuable for the synthesis of chiral ethers under mild conditions as, for example, in the preparation of alkoxyallenes via the initial formation of chiral propargyl ethers [8]. It has been proposed that a combination of 18-crown-6 and tetra-*n*-butylammonium iodide provide the best conditions for the *O*-benzylation of diethyl tartrate with 99% retention of optical purity [9].

A detailed study of the formation of *n*-octyl ethers under solid:liquid two-phase conditions in the absence of an added solvent has been reported [10]. Potassium alkoxides tend to produce higher yields of the ethers than do the corresponding sodium derivatives, but octene is the major product in the reaction of 1-bromooctane with potassium *t*-butoxide. High temperatures also tend to promote the preferential formation of octene and slightly higher yields of the ethers are obtained using *n*-octyl tosylate in preference to *n*-octyl bromide. β -Fluorinated acetals have been prepared either under basic catalytic liquid:liquid or solid:liquid conditions from the fluorinated alcohol and dichloromethane [11] with displacement of the fluorine atoms.

The highly hydrophilic alcohols, pentaerythritol and 2-ethyl-2-hydroxymethylpropan-1,3-diol, can be converted into their corresponding ethers in good yields under phase-transfer catalytic conditions [12]. Etherification of pentaerythritol tends to yield the trialkoxy derivative and kinetics of the reaction have been shown to be controlled by the solubility of the ammonium salt of the tris-ether in the organic phase and the equilibrium between the tris-ether and its sodium salt [13]. Total etherification of the tetra-ol is attained in good yield when reactive haloalkanes are used, and tetra-*n*-octylammonium, in preference to tetra-*n*-butylammonium, bromide [12, 13].

ω -Hydroxyalkyl vinyl ethers undergo the Williamson reaction with propargyl halides to yield vinyl propargyl diethers, $\text{CH}_2=\text{CHO}(\text{CH}_2)_n\text{OCH}_2\text{C}\equiv\text{CH}$, (66–90%) without any side reaction [14]. Epichlorohydrin reacts with benzyl alcohol under basic liquid:liquid two-phase conditions to form the benzyl ether without opening the epoxide ring [15]. Similarly, oligoethylene glycols react with epichlorohydrin to yield oxirane precursors for polymerization [16].

O-Allyl derivatives of a range of cyanhydrins have been obtained from the liquid:liquid two-phase reaction catalysed by Aliquat at 0 °C [17]. Yields range from *ca.* 25% to 45%.

3.1.1 Catalysed Williamson synthesis of ethers

Method A: The alcohol (0.5 mol) and TBA-I (1.0 g, 2.7 mmol) in petroleum ether (b.p. 50–70 °C, 200 ml) are stirred with aqueous NaOH (50%, 120 ml) at room temperature for 15–30 min. Me_2SO_4 (75.5 g, 0.6 mol) is then added dropwise with cooling over 1 h at such a rate that the reaction temperature is <45 °C, and the mixture is then stirred for a further 2–3 h. Aqueous NH_3 (d. 0.88, 10 ml) is added and the mixture is stirred for 30 min at room temperature and then poured into H_2O (100 ml). The organic phase is separated, washed with H_2O (2 \times 25 ml), dried (Na_2SO_4), and evaporated to give the methyl ether.

Method B: The haloalkane (20 mmol) and alcohol (20 mmol) in PhH (20 ml) are stirred vigorously with TBA-Br (0.32 g, 1 mmol) in aqueous NaOH (50%, 20 ml) for 2.5–3.5 h. The organic phase is separated, washed well with H_2O , dried (MgSO_4), and evaporated to yield the ether.

Method C: Aqueous NaOH (50%, 40 ml), the alcohol (0.1 mol), TBA- HSO_4 (5 mmol) and an excess of the alkyl halide (*ca.* 2.0 mol used as the organic solvent) are stirred together (see Table 3.1 for reaction time and temperature). On completion of the reaction the organic phase is separated, washed well with H_2O and evaporated. The residue is extracted with Et_2O (3 \times 15 ml) and the extracts are fractionally distilled to yield the dialkyl ether.

Method D: The preformed sodium alkoxide (25 mmol), Aliquat (0.2 g, 0.5 mmol) and *n*- $\text{C}_8\text{H}_{17}\text{Br}$ (1.93 g, 10 mmol) are stirred for 10 min and then allowed to stand until the reaction is complete. Et_2O (50 ml) is added and the mixture is filtered through Florisil. Evaporation of the filtrate yields the product.

Method E: The alcohol (25 mmol), powdered KOH or NaOH (25 mmol), and Aliquat (0.2 g, 0.5 mmol) are stirred for 10 min and *n*- $\text{C}_8\text{H}_{17}\text{Br}$ (1.93 g, 10 mmol) is then added. The reaction mixture is worked up to yield the alkyl octyl ether as described in 3.1.1.D.

Method F. Under microwave irradiation: The alcohol (10 mmol), haloalkane (25 mmol),

TABLE 3.1
Selected examples of the catalysed Williamson synthesis of aliphatic ethers

Alcohol	Alkylating agent	Reaction conditions	% yield
MeOH	<i>n</i> -C ₈ H ₁₇ Br	3.1.1.E/20°C/20 h	92 ^a
MeOH	<i>n</i> -C ₈ H ₁₇ Br	3.1.1.E/20°C/2 h	100
MeOH	<i>n</i> -C ₈ H ₁₇ Br	3.1.1.D/20°C/20 h	87 ^b
EtOH	<i>n</i> -C ₈ H ₁₇ Br	3.1.1.E/20°C/20 h	80 ^c
EtOH	<i>n</i> -C ₈ H ₁₇ Br	3.1.1.E/20°C/20 h	92 ^d
EtOH	<i>n</i> -C ₈ H ₁₇ Br	3.1.1.D/20°C/2 h	86 ^e
<i>n</i> -BuOH	PhCH ₂ Cl	3.1.1.C/35°C/1.5 h	92
<i>n</i> -C ₅ –C ₈ alcohols	(MeO) ₂ SO ₂	3.1.1.A/<45°C	~90
<i>n</i> -C ₈ H ₁₇ OH	<i>n</i> -BuCl	3.1.1.C/65°C/4 h	95
<i>n</i> -C ₈ H ₁₇ OH	<i>n</i> -C ₈ H ₁₇ Br	3.1.1.E/20°C/2 h	98
<i>t</i> -BuCH ₂ OH	(MeO) ₂ SO ₂	3.1.1.A/<45°C	70
<i>t</i> -BuOH	<i>n</i> -C ₈ H ₁₇ Br	3.1.1.D/20°C/36 h	35 ^f
PhCH ₂ OH	(MeO) ₂ SO ₂	3.1.1.A/<45°C	92
PhCH ₂ CH ₂ OH	(MeO) ₂ SO ₂	3.1.1.A/<45°C	90
PhCH=CHCH ₂ OH	(MeO) ₂ SO ₂	3.1.1.A/<45°C	90
MeCH(C ₃ H ₇)OH	(MeO) ₂ SO ₂	3.1.1.A/<45°C	60
MeCHOHCH ₂ OMe	<i>n</i> -BuCl	3.1.1.C/65°C/3 h	97
PhCHOHMe	(MeO) ₂ SO ₂	3.1.1.A/<45°C	93
PhCHOHCCl ₃	(MeO) ₂ SO ₂	3.1.1.A/<45°C	86
PhMe ₂ COH	(MeO) ₂ SO ₂	3.1.1.A/<45°C	85
Ph ₃ COH	(MeO) ₂ SO ₂	3.1.1.A/<45°C	80
(HC≡C) ₂ CBuOH	(MeO) ₂ SO ₂	3.1.1.A/<45°C	95
(HC≡C) ₂ CPhOH	(MeO) ₂ SO ₂	3.1.1.A/<45°C	97
CH ₂ =CHCH ₂ OH	PhCH ₂ Cl	3.1.1.C/30°C/12 h	72
<i>n</i> -BuO(CH ₂) ₂ OH	cyclo-C ₆ H ₁₁ Cl	3.1.1.C/70°C/7 h	0 ^g

^a + 7% octene. ^b + 13% octene. ^c + 4% octene and 15% unchanged halide. ^d + 5% octene. ^e + 10% octene. ^f + 53% octene (33% ether + 63% octene at 60°C over 6 h). ^g only cyclohexene (50%) formed.

Aliquat (0.81 g, 2 mmol) and powdered KOH (1.6 g) are stirred in a Pyrex reactor vessel and subjected to microwave irradiation at 30–60 W for 10–15 min. The mixture is filtered and the ether is isolated as described in 3.1.1.C.

3.1.2 Reaction of epichlorohydrin with alcohols

The glycol (50 mmol) or alcohol (0.1 mol) is added dropwise with stirring to epichlorohydrin (27 g, 0.3 mol), TBA-HSO₄ or TEBA-Cl (5 mmol), powdered NaOH (12 g), and H₂O (1.2 ml) while maintaining the temperature <45°C. The mixture is stirred for 40 min at ca. 40°C and then filtered. The solid is washed with CH₂Cl₂ (2 × 30 ml) and the dried (MgSO₄) organic solution is fractionally distilled to yield the glycidyl ether e.g. [(C₂H₃O)CH₂OCH₂]₂, 45%; [(C₂H₃O)CH₂O(CH₂)₂]₂O, 68%.

The Williamson alkylation of benzoin and deoxybenzoin, using procedure 3.1.1.B, produces dialkoxystilbenes and alkoxystilbenes (>90%), respectively, together with lesser amounts of C,O-dialkylated and C-alkylated derivatives [18]. The yields are

sensitive to the alkylating agent used, e.g. diethyl sulphate produces diethoxystilbene (92%) from benzoin, whereas only 30% is obtained when bromoethane is used; the major products are the C- and C,O-alkylated derivatives.

Although alcohols are oxidized by tetra-*n*-butylammonium persulphate when the reaction is conducted in dichloromethane, tetrahydropyranyl ethers have been produced (>90%) when attempts to oxidize the alcohol are conducted in tetrahydropyran (see Chapter 10) [19]. Tetrahydrofuranyl ethers have been prepared by an analogous method [20,21]. Base-mediated elimination of halo acids from β -halo alcohols under phase-transfer catalysed conditions produce oxiranes in high yield (70–85%). The reaction has particular use in the synthesis of epihalohydrins from β,γ -dihalo alcohols [22].

3.1.3 Oxiranes from β -halo alcohols

The β -bromo (or chloro) alcohol (50 ml) in PhH (330 ml) is refluxed with aqueous NaOH (29%, 17 ml) and TEBA-Cl (3.3 g, 18 mmol) for 0.5–1 h. The cooled organic phase is separated, washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the oxirane, which can be purified by chromatography.

The mild phase-transfer catalytic procedure is ideal for the facile synthesis of glycosidyl ethers. For example, the formation of mono-ethers has been reported for benzylidene protected glycopyranosides in yields in excess of 90% for methylation and benzylation [23–25], although it has also been shown that selective 2'-*O*-methylation of *N*⁶-cyclohexyladenosine is possible by phase-transfer catalysis without prior protection of other hydroxyl groups [26]. Regioselective benzylation of the 5-hydroxyl group of D-gluc- and D-mannofuranose derivatives [27], and complete *O*-butylation (87–95%) of a range of pyranosides [28], catalysed by the addition of tetra-*n*-butylammonium bromide, have been recorded. Benzyl ethers have also been obtained from preformed sodium salts of the glycopyranoside [29] and, when dichloromethane or dibromomethane is used as the alkylating agents and adjacent hydroxyl groups are unprotected, it is possible to form acetals [30]; if primary hydroxyl groups are unprotected, the bis(glycosidyl)methanes are formed [23, 30]. Maximum yields of the intramolecular acetals are obtained when a high reaction temperature is maintained [30]. A one-pot saponification of *O*-acetyl- Δ^2 -glycosides and subsequent *O*-benzylation (3.1.4.D) has been reported [31]. Hemiketals are *O*-methylated under standard solid:liquid phase-transfer catalytic conditions [32].

3.1.4 Glycosidyl ethers

Method A: An excess of the alkylating agent (15 mmol) is added to the glycoside (5 mmol) and TBA-Br (0.16 g, 0.5 mmol) in PhH (20 ml). Aqueous NaOH (50%, 20 ml) is added and the mixture is stirred at *ca.* 20°C until the reaction is complete, as shown by TLC analysis. The organic phase is separated, washed with H₂O (2 \times 25 ml), dried (MgSO₄), and evaporated to yield the glycosidyl ether.

Method B: Aqueous NaOH (5%, 5 ml) is added to the glycoside (3.5 mmol), TBA-HSO₄

(0.24 g, 0.7 mmol) and PhCH_2Br (0.72 ml, 60 mmol) in CH_2Cl_2 (60 ml) and the mixture is heated under reflux for *ca.* 48 h. When the reaction is complete, as shown by TLC analysis, the organic phase is separated, washed well with H_2O , dried (Na_2SO_4), and evaporated to yield the benzylated glycoside.

Method C: NaH as 50% dispersion in oil (3.7 g, 152 mmol) is added at 0°C to the protected glycopyranoside (150 mmol) in dry THF (250 ml) under N_2 with vigorous stirring. After *ca.* 2 h, TBA-I (0.55 g, 1.5 mmol) and PhCH_2Cl (19 g, 150 mmol) is added and the mixture is stirred at 20°C for *ca.* 3 h. The mixture is filtered through a pad of Florisil and evaporated to yield the O-benzylated product.

Method D from O-acetyl derivatives: The O-acetyl glycoside (65 mmol) in MeOH (80 ml) is added to methanolic NaOMe, prepared from Na (0.2 g) in MeOH (20 ml). The solution is stirred at 25°C for 24 h, evaporated to dryness, and the residue is dissolved in PhMe (50 ml) and aqueous NaOH (50%, 75 ml) containing TBA-Br (4.19 g, 13 mmol). The mixture is stirred at 60°C for 15 min and PhCH_2Cl (18.1 g) in MeOH (10 ml) is added dropwise and the mixture is heated for a further 5 h at 60°C and then evaporated. The residue is taken up in CH_2Cl_2 (50 ml), which is then washed with dilute HCl (0.1 M, 2×30 ml), brine (2×30 ml), dried (Na_2SO_4), and evaporated to yield the O-benzyl glycoside.

3.1.5 Glycosidyl acetal formation

Aqueous NaOH (50%, 80 ml) is added to a vigorously stirred solution of the glycoside (5 mmol) and TBA-Br (0.16 g, 0.5 mmol) in CH_2Br_2 (50 g) at 60 – 65°C . The reaction is monitored by TLC and, on completion, the organic phase is separated, washed well with H_2O , dried (MgSO_4), and evaporated to yield the acetals (replacement of CH_2Br_2 by CH_2Cl_2 and reaction temperatures of 25 – 35°C allows the formation of intermolecular acetals, but not intramolecular acetals).

3.1.6 Methylation of hemiketals

Powdered NaOH (0.4 g), MeI (1.41 g, 10 mmol), and TBA-I (37 mg, 10 mmol) are added to the hemiketal (1 mmol) in PhH (15 ml) and the mixture is stirred at room temperature for 1 h. H_2O (50 ml) is added and the organic phase is separated, washed well with H_2O and brine, dried (MgSO_4), and evaporated to yield the ketal (>90%).

Serine esters can be O-alkylated without concomitant N-alkylation, when the amino group is protected as its trityl derivative. The reaction is generally high yielding under relatively mild conditions [33], particularly with the more reactive allyl and benzyl halides.

3.1.7 O-Alkylation of serine esters

TEBA-Cl (3.03 g, 13.3 mmol), the alkylating agent (14.6 mmol), and aqueous NaOH (40%, 1.73 ml) are added to N-trityl serine ethyl ester (5.0 g, 13.3 mmol) in CH_2Cl_2 (5 ml) at 10°C . The mixture is warmed to room temperature and stirred vigorously for 18 h. The organic phase is separated, washed well with H_2O until the washings are neutral, dried (MgSO_4), and evaporated to yield the O-alkyl ether (84% from 4- $\text{FC}_6\text{H}_4\text{CH}_2\text{Br}$; 85% from $\text{CH}_2=\text{CHCH}_2\text{Br}$; 82% from $\text{Me}_2\text{C}=\text{CHCH}_2\text{Br}$; 84% from E- $\text{MeOCH}_2\text{CH}=\text{CHCH}_2\text{Br}$).

N,N-Dialkylhydroxylamines and oximes are readily alkylated to produce *O*-alkyl ethers [34–36] and oximes also react rapidly with dichloromethane to form the methylene dioximes [36–38]. *O*-Benzylhydroxylamine can be prepared on a large scale by alkylation of *N*-hydroxyphthalimide under phase-transfer catalytic conditions and subsequent solvolysis of the imide system [39].

3.1.8 *O*-Alkylation of *N,N*-dialkylhydroxylamines

The alkylating agent (10 mmol) in PhH (5 ml) is stirred under N₂ at *ca.* 80°C with Et₂NOH (0.6 g, 10 mmol) and TBA-Br (0.26 g, 0.8 mmol) in aqueous NaOH (50%, 3 ml) until the reaction is complete as shown by TLC. The aqueous phase is separated and extracted with PhH (2 × 5 ml) and the combined organic solutions are washed well with H₂O, dried (MgSO₄), and evaporated to yield the *O*-alkylated products (e.g. 98% after 4 h from PhCH₂Br; 62%, 4 h, PhCH₂Cl; 50%, 24 h, *n*-C₄H₉Br; 80% from 4-NO₂C₆H₄CH₂Br after 1 h at 25°C).

3.1.9 *O*-Benzylhydroxylamine

N-Hydroxyphthalimide (51.9 g, 0.318 mol) is added over a period of 5 h to aqueous NaHCO₃ (7.5%, 850 ml), PhCH₂Cl (44.3 g, 0.35 mol), and TBA-HSO₄ (10.8 g, 31.8 mmol) in refluxing CH₂Cl₂ (425 ml) with vigorous stirring. The mixture is refluxed for a further 2 h and then cooled to room temperature. The organic phase is separated and the aqueous phase is extracted with CH₂Cl₂ (2 × 80 ml). The combined organic solutions are washed sequentially with aqueous NaHCO₃ (5%, 2 × 200 ml), aqueous HCl (0.05 %, 2 × 200 ml), aqueous NaHCO₃ (5%, 200 ml) and H₂O (200 ml). The dried (Na₂SO₄) solution is evaporated to give the *N*-benzyloxyphthalimide (84%) which, upon hydrolysis with conc. aqueous HCl and AcOH, yields the *O*-benzylhydroxylamine (65% from the hydroxyphthalimide).

3.1.10 *O*-Alkylation of oximes

Aqueous NaOH (10%, 5 ml) is added to the haloalkane (4 mmol) and TBA-Br (0.1 g, 0.3 mmol) in PhH (2 ml). The mixture is stirred for 20 h at room temperature and then diluted with Et₂O (5 ml). The organic phase is separated, washed well with H₂O and aqueous NH₄Cl (5%), dried (Na₂SO₄), and evaporated to yield the *O*-alkyl oxime (Table 3.2).

3.1.11 Methylene dioximes

Aqueous NaOH (50%, 4 ml) is added dropwise to the oxime (30 mmol) and TBA-HSO₄ (0.6 g, 2 mmol) in CH₂Cl₂ (110 ml) at 0°C. The mixture is stirred at 25°C for *ca.* 4 h and H₂O (100 ml) is then added. The organic phase is separated and the aqueous phase is extracted with CH₂Cl₂ (2 × 25 ml). The combined organic solutions are washed until neutral with H₂O and then with brine, dried (Na₂SO₄), and evaporated to yield the methylene dioxime (Table 3.3).

Dialkyl peroxides, which are normally difficult to prepare by standard methods, can be conveniently synthesized by the catalysed reaction of alkyl peroxides and

TABLE 3.2
Selected examples of O-alkyl oximes

R ¹ R ² C=NOH	R ³ Br	% yield R ¹ R ² C=NOR ³
R ¹ = Ph R ² = H	<i>n</i> -BuBr	58
	CH ₂ =CHCH ₂ Br	76
Ph Me	<i>n</i> -BuBr	84
	CH ₂ =CHCH ₂ Br	86
<i>n</i> -C ₆ H ₁₃ Me	<i>n</i> -BuBr	80
	CH ₂ =CHCH ₂ Br	83
R ¹ , R ² = -(CH ₂) ₅ -	<i>n</i> -BuBr	60
	CH ₂ =CHCH ₂ Br	78

TABLE 3.3
Selected examples of methylene dioximes (R₂C=NO)₂ CH₂

R ¹ R ² C=NOH		% yield of	R ¹ R ² C=NOH		% yield of
R ¹	R ²	methylene dioxime	R ¹	R ²	methylene dioxime
Me	Me	53	4-MeOC ₆ H ₄	Me	90
Et	Et	50	4-ClC ₆ H ₄	Me	50
-(CH ₂) ₅ -		79	4-O ₂ NC ₆ H ₄	Me	95
cyclo-C ₃ H ₅	cyclo-C ₃ H ₅	57	2-thienyl	Me	89
Ph	H	91	4-MeC ₆ H ₄	<i>t</i> -Bu	90
Ph	Me	85	Ph	Ph	81

primary bromoalkanes [40]; secondary bromoalkanes fail to react. Although the generality of the procedure has not been explored in detail, it has been shown that, in favourable circumstances, allyl bromides react with *t*-butyl peroxide to yield the corresponding allyl *t*-butyl peroxide [41]. Polyethers have also been shown to catalyse the reaction, although S_{N2'} reactions also occur under such conditions. Symmetrical dialkyl peroxides can be obtained by the solid:liquid phase-transfer catalysed reaction of potassium dioxide with haloalkanes [42]. Yields are generally good (>70% for higher mass alkyl groups) with a high degree of purity (>90%).

3.1.12 Dialkyl peroxides

Method A: DMF (60 ml) is added to KO₂ (2.35 g, 33 mmol) and TEA-Br (3.36 g, 16 mmol) under anhydrous conditions under N₂. The mixture is stirred for 10 min and the haloalkane (10 mmol) is then added and the mixture stirred for a further 2–3 h at 20°C. Brine (50 ml) is added cautiously followed by *n*-C₆H₁₄ (100 ml). The organic phase is washed with H₂O (50 ml) and the aqueous phase is extracted with *n*-C₆H₁₄ (50 ml). The combined organic solutions are dried (Na₂SO₄) and evaporated to yield the peroxide, RO₂R (e.g. R = *n*-Bu, 45%; CH₂=CHCH₂, 55%; *n*-C₆H₁₄, 55%; *n*-C₈H₁₈, 73%; *n*-C₁₀H₂₂, 77%; *n*-C₁₄H₃₀, 80%; *n*-C₁₆H₃₄, 92%).

Method B: *t*-BuO₂H (14.6 g, 0.1 mol) and bromoalkane (0.1 mol) in CH₂Cl₂ (70 ml) are added dropwise to powdered KOH (5.6 g) and TEBA-Cl (2.28 g, 10 mmol) in CH₂Cl₂

(100 ml) at 15°C. The mixture is stirred at room temperature for *ca.* 9 h (the reaction is monitored by NMR spectral analysis) and the organic solution is then decanted from the solid and concentrated to an oil. The solid is dissolved in H₂O (25 ml) and extracted with *n*-C₅H₁₂ (3 × 25 ml). The extracts and the oil are combined and washed well with aqueous NaOH (10%) and brine, dried (Na₂SO₄), and evaporated to yield the dialkyl peroxide, *t*-BuO₂R, which is distilled under reduced pressure (e.g. R = *n*-Bu, 38%; CH₂=CHCH₂, 55%; MeCH=CHCH₂, 63%; Me₂C=CHCH₂, 62%).

3.1.13 Alkyl 2-*t*-butylperoxymethylpropenoates

The appropriate alkyl 2-bromomethylpropenoate (1 mol) TEBA-Cl (2.3 g, 10 mmol), and *t*-BuO₂H (90%, 110 g, 1.1 mol) in CH₂Cl₂ (150 ml) are stirred at –10°C. Powdered KOH (56 mg, 1.1 mol) is added portionwise such that the reaction temperature does not exceed –5°C. On complete addition of the hydroxide, the mixture is stirred at –5°C for 30 min and then allowed to come to room temperature and stirred for a further 1 h. The mixture is filtered and evaporated under reduced pressure. *n*-C₅H₁₂ (200 ml) is added to the residue and the organic solution is filtered, washed with H₂O (100 ml), dried (MgSO₄), and evaporated to yield the peroxide (ethyl ester, 92%; menthyl ester, 85%; *t*-butyl ester, 45%).

Many examples can be found for the preparation of silyl ethers under phase-transfer catalytic procedures. Typical methods involve the reaction of the alcohol with a trialkylsilyl halide and yields are generally in excess of 85% [see, e.g. 43]. Milder neutral conditions for silylation are often preferable with acid-sensitive substrate. Such silyl protection of alcohols has been achieved using *O,N*-bis(trialkylsilyl)acetamide catalysed by tetra-*n*-butylammonium fluoride [44–46]. Although the ammonium fluoride is frequently used to cleave O–Si bonds, its use in catalytic amounts is advantageous for the silylation reactions. Selective silylation of hydroxyl groups (relative rates: primary > secondary > tertiary) can be controlled by choice of solvent (less selectivity possibly due to migration of the silyl groups in more polar solvents) and hydroxyl groups are preferentially silylated in the presence of amino and carboxyl groups. Silylation of alcohols (>90%), catalysed by the ammonium fluoride, using *N,N'*-bis(trimethylsilyl)urea, trialkylsilanes or hexamethyldisilanes has also been reported [47].

3.1.14 Trialkylsilyl ethers (Table 3.4)

Method A: The alcohol (0.1 mol), *t*-BuMe₂SiCl (16.5, 0.11 mol) and Aliquat (0.4 g, 1 mmol) in petroleum ether or PhMe (10 ml) are added to anhydrous K₂CO₃ (15 g, 0.11 mol) and the mixture is stirred at 80°C for 6 h. The mixture is filtered and fractionally distilled to yield the ether.

Method B: The alcohol (0.1 mol), and Aliquat (0.4 g, 1 mmol) in petroleum ether or PhMe (10 ml) are added to anhydrous K₂CO₃ (15 g, 0.11 mol) and Me₃SiCl (12 g, 0.11 mol) and the mixture is stirred for 4 h at 60°C. The ether is isolated as described in 3.1.14.A.

Method C: The carbonyl compound or alcohol (1 mol) is added to TBA-F (7.8 g, 30 mmol) and Me₃SiCH₂CO₂Et (132.24 g, 1 mol) under argon. The slightly exothermic

TABLE 3.4
Selected examples of trialkylsilyl ethers

Alcohol	Method	% yield of Me ₃ SiOR	Alcohol	Method	% yield of <i>n</i> -BuMe ₂ SiOR
<i>n</i> -C ₈ H ₁₇ OH	3.1.14.B	98	<i>n</i> -C ₆ H ₁₃ OH	3.1.14.A	89
<i>n</i> -C ₁₀ H ₂₁ OH	3.1.14.B	98	PhCH ₂ OH	3.1.14.B	88
<i>n</i> -C ₁₂ H ₂₅ OH	3.1.14.B	91		3.1.14.E	96
<i>n</i> -C ₁₆ H ₃₃ OH	3.1.14.B	72	PhCMe ₂ OH	3.1.14.E	97 ^a
Ph(CH ₂) ₃ OH	3.1.14.C	92	PhCHOHCH ₂ OH	3.1.14.E	95 ^{b,c}
EtCHMeOH	3.1.14.B	91	MeCHOH(CH ₂) ₄ OH	3.1.14.E	98 ^d
PhC(<i>i</i> -Pr) ₂ OH	3.1.14.C	92			
cyclo-C ₆ H ₁₁ OH	3.1.14.B	81			
PhCH ₂ OH	3.1.14.A	88			

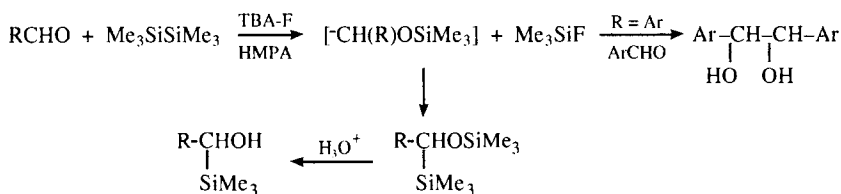
^a 16 h reaction in NMP. ^b Disilylation. ^c Reaction in CH₂Cl₂ leads to a 2 : 1 : 1 mixture of primary:secondary:bis silylation. ^d Monosilylation of primary hydroxyl group after 24 h.

reaction is stirred for 1–3 hours at room temperature and then diluted with *n*-C₆H₁₄ (50 ml), filtered, and fractionally distilled to yield the trimethylsilyl ether.

Method D: TBA-F (26 mg, 0.1 mmol) is added to Me₃SiSiMe₃ (0.2 g, 1.5 mmol) in HMPA (2 ml) and the solution is stirred for 5 min at room temperature. The solution is then added to the aldehyde and the mixture is stirred for 4–5 h. On completion of the reaction, HCl:MeOH (1 : 10, 1 ml) is added and the mixture is extracted with Et₂O (3 × 35 ml). The extracts are washed with aqueous NH₄Cl (sat. soln. 25 ml) and brine (25 ml), and concentrated under vacuum. Chromatography from silica gives the trimethylsilyl enol ether or, in the case of the aryl aldehydes, the pinacol.

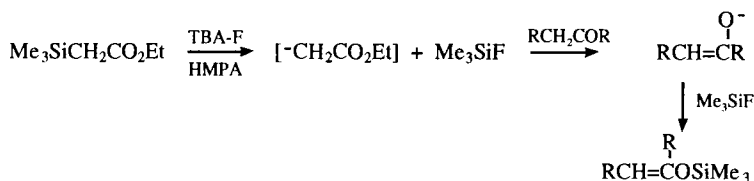
Method E: The alcohol (0.1 mol) and the appropriate *O,N*-bis(trialkylsilyl)acetamide (60 mmol) and TBA-F.3H₂O (4.73 g, 15 mmol) are stirred in THF (50 ml) at room temperature for 30–90 min. On completion of the reaction, the mixture is filtered and concentrated, the residue is titrated with Et₂O (3 × 25 ml) and the combined ethereal solutions are evaporated to yield the silylated product.

Trimethylsilylation of enolizable carbonyl compounds and alcohols has also been accomplished by the fluoride ion promoted reaction with hexamethyldisilane and ethyl trimethylsilylacetate [48, 49], with high stereospecificity giving *Z*-enol ethers from ketones [50]. 1-Trimethylsilyl-(1-trimethylsilyloxy)alkanes, produced from the reaction of aldehydes with hexamethyldisilane, undergo acid-catalysed hydrolysis during work up to yield the trimethylsilylcarbinols [51]. In the case of aryl aldehydes, the initially formed trimethylsiloxy carbanion produces the pinacol (Scheme 3.1).



Scheme 3.1

Silylation using the silylacetate (**3.1.14**) [49] involves the initial formation of the acetate carbanion, which abstracts a proton from the carbonyl compound or alcohol (Scheme 3.2, Table 3.5). When the reaction with a ketone is conducted in the presence of an aldehyde, crossed aldol products are obtained (see Chapter 6).



Scheme 3.2

TABLE 3.5

Trimethylsilylation of enolizable ketones using ethyl trimethylsilylacetate^a

Ketone	% yield of enol ether	Ketone	% yield of enol ether
PhCOMe	98	Et ₂ CO	100 ^b
Cyclopentanone	74	<i>n</i> -Bu ₂ CO	91 ^b
Cyclohexanone	98		
Cyclooctanone	86	2-Methylcyclohexanone	A 80 ^c
Cyclododecanone	94		B 20

^a **3.1.14.C**. ^b Z-enol ether. ^c A = 1-Me₃SiO-6-Me-cyclohex-1-ene; B = 1-Me₃SiO-2-Me-cyclohex-1-ene after reaction at -78°C for 5 h. A:B ratio = 7:3 (0°C, 2 h) and 4:6 (in refluxing THF).

Intramolecular cyclization of 5-trimethylsilyloxy mesylates to produce 6-membered cyclic ethers is catalysed by tetra-*n*-butylammonium fluoride on a stoichiometric scale [52] and has found particular application in a high yielding (>90%) synthesis of *O*-2-isocephams.

Oxiranes undergo ring opening with trialkylsilyl chlorides to yield trialkylsilyl chloroethyl ethers [51]. The reaction has been shown to be catalysed by tetra-*n*-butylammonium chloride, although most studies have used triphenylphosphine as the catalyst. Substituted oxiranes are cleaved by haloalkanes to yield the corresponding 1-chloro-2-alkoxy-2-substituted alkanes [52] (see Section 9.3).

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3.2 ALKYLATION OF PHENOLS AND ENOLS

The greater acidity of phenols results in milder alkylation conditions. The majority of procedures are generally conducted as liquid:liquid two-phase systems and do not always require highly basic media [e.g. 1–5]. Inspection of Table 3.6 clearly indicates that the reactions are not subject to steric hindrance nor are they influenced greatly by the electronic character of substituents on the aromatic ring. Early studies established that, under the liquid:liquid two-phase conditions, the choice of solvent and catalysts affected the rate of reaction of phenoxide ions with *n*-butyl halides [2]. However, it has also been shown that phenol reacts with the most commonly used solvent, dichloromethane, or more rapidly with dibromomethane under solid:liquid phase-transfer catalysed conditions [6,7]. Single phase reactions where the alkylating agent is used as the organic phase are frequently reported [e.g. 8, 9] and the procedure has been applied with some success to the alkylation of readily oxidized hydroquinone and 4-aminophenol, the latter yields a mixture of the ether, as the major product, together with the *N,O*-dialkylated derivative [9]. Polymer-supported ammonium catalysts [10–13] have been used to form, for example, diaryloxymethanes, phenacyl ethers, aryloxyacetones, etc. Predictably, 2-hydroxycarbazole is alkylated under solid:liquid two phase conditions initially on the hydroxyl group, and subsequent reaction yields the *N,O*-dialkylated product [14].

It is noteworthy that, when 4-(chloroacetyl)phenols are *O*-benzylated with benzyl bromide under catalytic conditions, halogen exchange also occurs to give a 60:40 mixture of the 4-chloroacetyl- and 4-bromoacetyl phenyl ethers [15]. Also, when phenols react with 1-bromo-3-chloropropane in the presence of a quaternary ammonium catalyst, a mixture of (3-chloropropyl)- and (3-bromopropyl) phenyl ethers is obtained in overall yields of *ca.* 75% [16]. The ratio of the two ethers is governed by the choice of catalyst and, whereas only a *ca.* 2:1 ratio in favour of the chloropropyl ether is obtained when a bulky catalyst such as Adogen or a tetra-*n*-butylammonium salt is used, the chloropropyl ether predominates to the extent of >25:1 when less bulky catalysts, such as benzyltriethylammonium chloride, are used. The choice of the anion has only marginal effect. *gem*-Dichlorocyclopropanes having an electron-withdrawing group at the 2-position react with phenoxide anions to produce the diphenoxy derivatives [17].

A convenient catalysed two-phase methoxymethylation of phenols (>80%) has been described [18]. This is an improvement on the standard reaction, which normally requires anhydrous conditions. 1-Naphthol is reported to be *O*-methylated under catalytic conditions with only a minor amount (*ca.* 3%) of *C*-methylation at the 2-position [19].

The almost instantaneous intramolecular ether formation by reaction of phenoxy anions, generated from the silyl ethers with a stoichiometric amount of tetra-*n*-butylammonium fluoride, on mesylate esters has been used to synthesize labile benzo-*O*-2-isocephams (>90%) [20].

3.2.1 O-Alkylation of phenols and related compounds

Method A: The phenol (10 mmol) in aqueous NaOH (0.3 M, 50 ml) and the alkylating agent (30 mmol) in CH_2Cl_2 (50 ml) is shaken with TBBA-Br (36 mg, 0.1 mmol) at room temperature for 2–12 h. The organic phase is separated and the aqueous phase is extracted with CH_2Cl_2 (20 ml). The combined organic solution is evaporated and the residue is extracted with Et_2O . The extracts are washed sequentially with aqueous NH_3 (2M, 2×20 ml), aqueous NaOH (2M, 2×20 ml) and brine (20 ml), dried (Na_2SO_4) and evaporated to yield the aryl ether.

Method B: The phenol (0.05 mol) in aqueous NaOH (50%, 10 ml) is stirred at room temperature for *ca.* 50 min. The alkylating agent (0.05 mol) and TBA-Br (0.5 g, 1.5 mmol) are added and the mixture is heated for 4–8 h. H_2O (80 ml) is then added and the mixture is extracted with Et_2O (3×30 ml). The extracts are washed with H_2O (3×40 ml), dried (Na_2SO_4), and evaporated to yield the aryl ether.

Method C: CH_2Cl_2 or CH_3Br_2 (100 ml) and H_2O (100 ml) are added to the phenol (20 mmol), NaOH (1.2 g, 30 mmol) and TBA-Br (0.17 g, 0.5 mmol) and the mixture is shaken vigorously at room temperature for 4–5 h. The organic phase is separated and the aqueous phase is extracted with CH_2Cl_2 (2×40 ml). The combined organic solution is evaporated and the residue is extracted with Et_2O (3×20 ml). The extracts are washed sequentially with aqueous NaOH (2M, 2×20 ml), brine (2×20 ml), dried (Na_2SO_4), and evaporated to yield the ether.

Method D (solid:liquid conditions): The phenol (5 mmol), powdered KOH (0.3 g, 5 mmol) and Aliquat (40 mg, 0.1 mmol) are shaken together for 10 min at room temperature. The alkylating agent RBr (5 mmol) or $\text{Br}(\text{CH}_2)_n\text{Br}$ (2.5 mmol) is added and the mixture is shaken vigorously for a further 5 min at room temperature and then allowed to stand (time and temperature given in Table 3.6). The monoether is isolated by direct chromatography of the reaction mixture on Florosil. The diether is isolated by washing the reaction mixture with Et_2O (2×25 ml) and adding CH_2Cl_2 (100 ml) to the extracts before chromatography.

Method E (solid:liquid conditions): The alkylating agent (0.12 mol), TBA-Br (1.61 g, 5 mmol) and the phenol (0.1 mol) in MeCN (50 ml) are added to anhydrous K_2CO_3 (20 g) and the mixture is stirred at room temperature. On completion of the reaction, as shown by GLC analysis, H_2O (100 ml) is added and the aqueous mixture is extracted with EtOAc (3×25 ml). The combined extracts are washed with H_2O (2×25 ml), dried (MgSO_4), and evaporated to give the aryl ether.

Method F (polymer-supported reaction): Amberlite IRA-400 (ArO^- form) (5 g), obtained by washing the resin with aqueous ArONa (0.25 M, 100 ml), followed by H_2O (100 ml), is suspended in CH_2Cl_2 (20 ml) and refluxed for *ca.* 12 h.* The resin is removed by filtration and is washed with CH_2Cl_2 (25 ml). Evaporation of the combined organic solutions yields the diaryloxymethane (*phenols having electron-withdrawing substituents may require 15 h reaction time for maximum yield).

Method G: 2-Amino-3-hydroxypyridine (110 g, 1 mol) in CH_2Cl_2 (500 ml) is stirred with aqueous NaOH (40%, 500 ml), the alkylating agent (1.07 mol), and Adogen (5.3 g, 11.4 mmol) at 25°C for 16 h. The organic phase is separated, and the aqueous phase is diluted with H_2O (200 ml) and extracted with CH_2Cl_2 (3×300 ml). The combined organic solutions are dried (K_2CO_3) and evaporated to yield the 3-pyridyl ether [e.g. 71% from PhCH_2Cl ; 32% from $\text{Ph}(\text{CH}_2)_2\text{Cl}$; 33% from $\text{Ph}(\text{CH}_2)_3\text{Cl}$; 32% from PhCHMeCl ; 87% from 4- $\text{ClC}_6\text{H}_4\text{CH}_2\text{Cl}$; 74% from 2- $\text{FC}_6\text{H}_4\text{CH}_2\text{Cl}$; 72% from 4-*t*- $\text{BuC}_6\text{H}_4\text{CH}_2\text{Cl}$; 88% from 3- $\text{CF}_3\text{C}_6\text{H}_4\text{CH}_2\text{Cl}$; 43% from 2-pyridyl CH_2Cl ; 76% from 2-thienyl CH_2Cl]

TABLE 3.6
Selected examples of the catalysed Williamson synthesis of aryl ethers

Phenol	Alkylating agent	Reaction conditions	% yield
PhOH	Mel	3.2.1.A/rt	77
		3.2.1.E/rt	>96
	<i>n</i> -BuBr	3.2.1.A/rt	85
	cyclo-C ₃ H ₁₁ Br	3.2.1.A/rt	73
	CH ₂ =CHCH ₂ Br	3.2.1.E/rt	>90
	PhCHMeBr	3.2.1.A/rt	91
	BrCH ₂ CO ₂ Et	3.2.1.A/rt	86
	epichlorohydrin	3.2.1.A/rt	77
	CH ₃ Br ₂	3.2.1.D/24 h/25 °C	90
	Br(CH ₂) ₃ Br	3.2.1.D/24 h/80 °C	98
	Br(CH ₂) ₁₀ Br	3.2.1.D/14 h/85 °C	92
	Br(CH ₂) ₃ Cl	3.2.1.B/24 h/110 °C	80 ^a
	PhCH ₂ Cl	3.2.1.B/4 h/25 °C	97
	2,4-(O ₂ N) ₂ C ₆ H ₃ Cl	3.2.1.B/4 h/25 °C	82
2-MeC ₆ H ₄ OH	PhCOCH ₂ Br	3.2.1.B/4 h/25 °C	76
	CH ₂ Cl ₂	3.2.1.F/12 h/25 °C	91
2-allylC ₆ H ₄ OH	Mel	3.2.1.E/rt	>90
2-MeOC ₆ H ₄ OH	CH ₂ =CClCH ₂ Cl	3.2.1.B/8 h/25 °C	22
	CH ₂ =CHCH ₂ Br	3.2.1.C/5 h/60 °C	82
	2,4-(O ₂ N) ₂ C ₆ H ₃ Cl	3.2.1.B/5 h/25 °C	94
	PhCOCH ₂ Br	3.2.1.B/5 h/25 °C	51
4-MeOC ₆ H ₄ OH	(MeO) ₂ SO ₂	3.2.1.A/rt	91
2-O ₂ NC ₆ H ₄ OH	Mel	3.2.1.A/rt	81
	CH ₂ Cl ₂	3.2.1.F/15 h/25 °C	90
3-O ₂ NC ₆ H ₄ OH	Mel	3.2.1.A/rt	79
4-O ₂ NC ₆ H ₄ OH	Mel	3.2.1.A/rt	83
	CH ₂ Cl ₂	3.2.1.F/15 h/25 °C	92
1-Naphthol	epichlorohydrin	3.2.1.A/rt	42 ^b
	PhCOCH ₂ Br	3.2.1.B/4 h/25 °C	72
	CH ₂ Cl ₂	3.2.1.F/12 h/25 °C	92
2-Naphthol	Mel	3.2.1.A/rt	92
	(EtO) ₂ SO ₂	3.2.1.A/rt	81
	epichlorohydrin	3.2.1.A/rt	41
2,6-Me ₂ C ₆ H ₃ OH	Mel	3.2.1.A/rt	92
2,6-MeO ₂ C ₆ H ₃ OH	(MeO) ₂ SO ₂	3.2.1.A/rt	91
2,6- <i>t</i> -Bu ₂ C ₆ H ₃ OH	(MeO) ₂ SO ₂	3.2.1.A/rt	83
2,4,6- <i>t</i> -Bu ₃ C ₆ H ₂ OH	(MeO) ₂ SO ₂	3.2.1.A/rt	93
8-Hydroxyquinoline	EtBr	3.2.1.D/1 h/60 °C	78
	<i>n</i> -BuBr	3.2.1.D/1 h/85 °C	90
	<i>n</i> -C ₈ H ₁₇ Br	3.2.1.D/2 h/85 °C	90
	PhCH ₂ Cl	3.2.1.B/4 h/25 °C	90
	PhCOCH ₂ Br	3.2.1.B/4 h/25 °C	80
	CH ₂ =CHCH ₂ Br	3.2.1.B/4 h/25 °C	84
	2,4-(O ₂ N) ₂ C ₆ H ₃ Cl	3.2.1.C/4 h/70 °C	92
	Br(CH ₂) ₃ Br	3.2.1.D/1 h/60 °C	46
	Br(CH ₂) ₆ Br	3.2.1.D/1 h/60 °C	60
	Br(CH ₂) ₆ Br	3.2.1.D/1 h/60 °C	50

^a in toluene; 1.9 : 1 ratio of chloropropyl ether:bromopropyl ether. 71% using TEBA-Cl in toluene giving a 24.9 : 1 ratio of chloropropyl ether:bromopropyl ether. ^b + 20% di(1-naphthoxy)methane.

In addition to the glycidyl ethers, derived from epichlorohydrin, cited in Table 3.6, a range of analogous ethers, which are useful precursors in the synthesis of cardiovascular drugs, have been obtained under solid:liquid two-phase conditions [21]. The procedure has some advantages over the liquid:liquid two-phase system in that reaction times can be reduced and yields are invariably >90%. Although tetra-*n*-butylammonium bromide is an effective catalyst, optimum yields were obtained using the tetra-*n*-butylammonium alkanesulphonate, $\text{Bu}_4\text{N}^+ \text{MeCHOHCH}_2\text{OSO}_3^-$.

3.2.2 Solid:liquid two-phase synthesis of aryl glycidyl ethers

The phenol (21.3 mmol), epichlorohydrin (0.17 mol), anhydrous K_2CO_3 (5.9 g, 42.6 mmol) and TBA- $\text{MeCHOHCH}_2\text{OSO}_3$ (0.2 g, 0.5 mmol) are stirred for 90 min at 75–80°C until the reaction is complete, as shown by TLC analysis. The mixture is cooled to room temperature and the mixture is filtered. The residue is washed with epichlorohydrin and the combined organic solution is fractionally distilled to yield the aryloxymethyloxirane (85–93%).

Polymeric aryl ethers have been obtained from, for example, bisphenol and 1,4-dichlorobut-2-ene or 1,4-bis(chloromethyl)benzene in a basic medium in the presence of tetra-*n*-butylammonium hydrogen sulphate [22].

3.2.3 Methylenedioxy arenes (dioxoles)

H_2O (20 ml), CH_2Br_2 (26 g, 0.15 mol) and Adogen (0.45 g, 1 mmol) are stirred and refluxed briefly under N_2 . The dihydroxyarene (0.1 mol) and aqueous NaOH are then added dropwise over a period of *ca.* 2 h. The mixture is stirred and refluxed for a further 1 h. The organic phase is separated and the extracts are washed well with aqueous NaOH (1M) and then with H_2O until the washings are neutral. The dried (MgSO_4) organic phase is evaporated to yield the dioxole [e.g. benzo-1,3-dioxole (76%) from catechol; naphtho-[2,3-*d*]-1,3-dioxole (82%) from 2,3-dihydroxynaphthalene; piperonal (80%) from 2,3-dihydroxybenzaldehyde; 4-methylbenzo-1,3-dioxole (86%) from 4-methylcatechol].

The resonance stabilization energy of the aromatic ring generally mitigates against C-alkylation, and quaternary ammonium catalysts promote *O*-alkylation. For example, 2-naphthol, which yields both the naphthyl ether and the C-1 alkylated derivative when lithium *t*-butoxide is used, produces only the *O*-naphthyl ether when Aliquat is used in a basic two-phase system in the absence of an added solvent [5]. Anthrone also yields 9-alkoxyanthracenes under phase-transfer catalysed alkylation [23]. The non-tautomeric 3-hydroxypyridine system is converted into *O*-alkyl derivatives [e.g. 24, 25], even when substituted by a 2-amino group (see 3.2.1.E) without alkylation of the amino group or quaternization of the pyridine ring [24]. For the corresponding reactions of the tautomeric 2- and 4-pyridones, see Chapter 5.3. *O*-Arylation of glucosides with inversion at the reactive site, e.g. with tetra-*O*-benzylglucopyranosyl bromides, tetra-*O*-acetylpyranosyl bromides, and acylaminoglycosyl chlorides, has been accomplished in moderate to good yield under liquid:liquid phase-transfer catalytic conditions [26–29]. Although there is no apparent rationale,

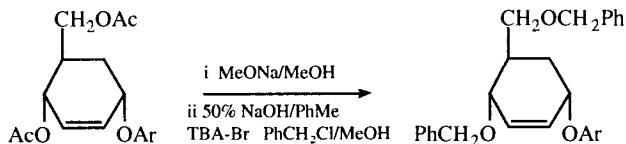
it appears that higher yields are obtained for galactose derivatives, compared with glucose derivatives.

3.2.4 Synthesis of *O*-aryl β -D-glucopyranosides

Method A: The glucopyranosyl bromide (1 mmol) in CH_2Cl_2 (10 ml) and H_2O (10 ml) is added to the phenol (3 mmol) and TEBA-Cl or Adogen (0.2 mmol) in aqueous KOH or NaOH (25 mmol) and the mixture is stirred at room temperature for 8–60 h. The organic phase is separated, washed with H_2O , dried (MgSO_4), and evaporated to yield the *O*-aryl derivative (68% from phenol; 60% from 2-cresol; 53% from 3-chlorophenol, 54% from 4-methoxyphenol; 56% from 4-nitrophenol; 57% from 1-naphthol; 44% from thiophenol; 36% from 8-hydroxyquinoline).

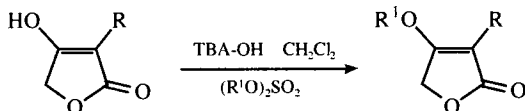
Method B: The glucopyranosyl bromide (24 mmol) in CHCl_3 (10 ml) is added to the phenol (48 mmol) and TEBA-Br (5.53 g, 20 mmol) in aqueous NaOH (1.25 M, 50 ml) and the mixture is stirred under reflux for *ca.* 3 h. The organic phase is separated, washed with aqueous NaOH (1.25 M, 2×50 ml), dried (MgSO_4), and evaporated to yield the *O*-aryl derivative.

Acetylglycosyl aryl ethers, obtained by the Ferrier reaction of acetylglycals with phenols, can be de-acetylated and converted into the benzyl ethers in a one-pot reaction in the presence of a quaternary ammonium salt (see, e.g. Scheme 3.3) [30].



Scheme 3.3

Unlike the *O*-alkylation of anthrone [23] and tetrone acids (Scheme 3.4) [31], the alkylation of potentially tautomeric β -dicarbonyl compounds under phase-transfer catalytic conditions has been studied in detail and, in virtually all examples cited, the *C*-alkylation products predominate [32–38]. *O*-Alkylation only appears to be an important reaction route, where there is steric hindrance to the approach of the alkylating agent to the carbanionic centre. It has also been shown that the optical purity of *O*-alkylated derivatives of ethyl acetoacetate, derived from a chiral alkylating agent under the influence of a phase-transfer catalyst retains its configuration to a greater extent than does the *C*-alkyl derivative. It has been suggested that the tetra-*n*-butylammonium cation may fragment and that tributylammonium cations become involved in some (unknown) way with the alkylation [39, 40].



Scheme 3.4

3.2.5 Regiospecific O-alkylation of tetronic acids

Me_2SO_4 or Et_2SO_4 (17.3 mmol) is added with vigorous stirring to the TBA-tetronate (16.5 mmol) prepared by the addition of aqueous TBA-OH (0.5 M, 3.5 ml) to the appropriate tetronic acid (16.5 mmol) and evaporation to dryness under reduced pressure, in CH_2Cl_2 (70 ml). The mixture is stirred until the reaction is complete and the solvent is then evaporated. H_2O (50 ml) is added to the residue and the aqueous solution is continuously extracted with Et_2O for ca. 3 h. The ethereal extract is washed with aqueous NaHCO_3 , dried (MgSO_4), and evaporated to give the 4-alkoxy-5H-furan-2-one ($\text{R} = \text{H}$, $\text{R}^1 = \text{Me}$ 58%, $\text{R}^1 = \text{Et}$ 78%; $\text{R} = \text{Me}$, $\text{R}^1 = \text{Me}$ 59%, $\text{R}^1 = \text{Et}$ 65%; $\text{R} = \text{Et}$, $\text{R}^1 = \text{Me}$ 65%, $\text{R}^1 = \text{Et}$ 88%; $\text{R} = \text{PhCH}_2$, $\text{R}^1 = \text{Me}$ 58%).

3-Hydroxycoumarins are alkylated under extremely mild basic liquid:liquid phase-transfer catalytic conditions to produce the ethers and 4-alkylated derivatives [41]. The major product tends to be the ether (50–60%) but the yield of the C-alkylated product is significant with allyl bromide and with propargyl bromide, where rearrangement of the allenic derivative occurs.

3.2.6 Alkylation of 3-hydroxycoumarin

TBA-Br (80 mg, 0.25 mmol) in aqueous NaOH (1%, 50 ml) is added to the 3-hydroxycoumarin (6 mmol) and haloalkane (12 mmol) in CH_2Cl_2 (50 ml) and the mixture is stirred at 50°C for 12 h. The organic phase is separated, washed with aqueous HCl (2 M, 3×50 ml) and brine (3×50 ml), dried (Na_2SO_4), and evaporated to yield the alkylated products, which can be separated by chromatography from silica.

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3.3 ESTER FORMATION AND RELATED REACTIONS

A new facile approach to the synthesis of esters involving the *O*-alkylation of tetramethyl ammonium carboxylate salts in dimethylformamide was reported in 1972 [1]. This was later improved as a catalytic process without loss of the high yields [see, e.g. 2–6]. Generally, aromatic carboxylic acids are less reactive than aliphatic acids and require more vigorous conditions [7] and, reflecting the different acidities of the two OH sites, only the carboxyl group of hydroxybenzoic acids are alkylated. In the absence of an alkylating agent, the carboxylate anions will react with dichloromethane, or dibromomethane, if used as the solvent [8]; terphthalic acid produces the expected polymer, but it is reported that phthalic acid and succinic acid do not react. The mild liquid:liquid phase condition is particularly suited for the esterification of acid- or base-labile acids or alcohols and has been used with success in, for example, the esterification of protected amino acids and peptides [9–11] and the preparation of acid-sensitive pyrrole carboxylates and pyrrolylmethyl esters [12, 13 and Jones, unpublished]. Acid-labile acetal bonds are also stable during catalysed esterification [e.g. 6]. Additionally, in contrast with classical procedures, alcohols which are susceptible to *E:Z*-isomerism retain their stereochemistry during esterification under phase-transfer catalysis [14].

Solid-liquid phase systems with no added solvent produce esters in high yield [e.g. 2, 3] and are particularly useful when using less reactive alkyl halides [e.g. 15], for the preparation of sterically hindered esters [16], or where other basic sites within the molecule are susceptible to alkylation, e.g. anthranilic acid is converted into the esters with minimal *N*-alkylation and pyridine carboxylic acids do not undergo quaternization [17]. Excellent yields of the esters in very short reaction times (2–7 minutes) are also obtained when the two-phase system is subjected to microwave irradiation [18]. Direct reaction of the carboxylic acids with 1,2-dichloroethane under reflux yields the chloroethyl ester [19], although generally higher yields of the esters are obtained under microwave conditions [20].

The combined catalysis by 18-crown-6 and tetra-*n*-butylammonium bromide produces higher yields in shorter reaction times than either of the catalysts separately (Table 3.7) [21] and almost quantitative yields have been reported for solid:solid:liquid triphase catalysed esterification using silica impregnated with tetramethylammonium chloride [22].

The process has also been adapted using resin supported catalysts [e.g. 23–28]. Generally, the reactivity of the alkyl halides follows the normal pattern of $I > Br > Cl$, but secondary alkyl halides are less reactive and require high reaction temperatures and tertiary alkyl halides fail to react.

TABLE 3.7

Combined crown ether and quaternary salt catalysis of the esterification of benzoic acid with phenacyl bromide

18-Crown-6	TBA-Br	Reaction conditions	% yield
0.0 mmol	0.05 mmol	rt/4 h	86
0.015 mmol	0.0 mmol	rt/3 h	90
0.015 mmol	0.1 mmol	rt/45 min	98
0.015 mmol	0.1 mmol	80°C/5 min	98

3.3.1 Esterification of aliphatic acids

Method A: The sodium carboxylate (2 mol) and Aliquat (10 g, 25 mmol) in an excess of the haloalkane (5 mol) are heated at *ca.* 100°C with vigorous stirring. Either (a) H₂O (350 ml) is added and organic phase system is separated, dried (Na₂SO₄), and fractionally distilled or (b) Et₂O (50 ml) is added to the cooled reaction mixture and the solution is filtered through a pad of Florosil and fractionally distilled to yield the ester.

Method B: The potassium salt of the carboxylic acid (11 mmol) is shaken with TBA-Br (0.1 mmol) or Aliquat (0.3 mmol) for 5 min. The haloalkane (10 mmol) is added and the mixture shaken for a further 5 min, and then allowed to stand (see Table 3.8). The mixture is filtered and Et₂O (50 ml) is added. The solution is filtered through silica (5 g) and evaporated to yield the ester.

Method C (methylene diesters): The acid (0.1 mol) and TBA-HSO₄ (33.9 g, 0.1 mol) in

TABLE 3.8
Selected examples of the phase-transfer catalysed formation of aliphatic esters

Acid	Haloalkane	Reaction conditions ^a	% yield
MeCO ₂ H	<i>n</i> -C ₄ H ₉ Br	3.3.1.A/5 h/100°C	95
		3.3.1.B ¹ /2 h/60°C	98
		3.3.1.B ² /8 h/rt	57 ^b
	<i>n</i> -C ₅ H ₁₁ Br	3.3.1.A/5 h/130°C	95
	<i>n</i> -C ₈ H ₁₇ Cl	3.3.1.B ¹ /2 h/85°C	64 ^c
	<i>n</i> -C ₈ H ₁₇ Br	3.3.1.B ¹ /2 h/60°C	73 ^d
		3.3.1.B ² /2 h/60°C	98
	<i>n</i> -C ₈ H ₁₇ I	3.3.1.B ¹ /6 h/85°C	33
		3.3.1.B ² /6 h/85°C	71 ^e
	<i>n</i> -C ₁₆ H ₃₃ Br	3.3.1.B ¹ /3 h/85°C	72
		3.3.1.B ² /3 h/85°C	98
	CH ₂ =CHCH ₂ Br	3.3.1.B ¹ /2 h/rt	94
		3.3.1.B ² /2 h/rt	98
	PhCH ₂ Br	3.3.1.B ¹ /1 h/rt	84
		3.3.1.B ² /2 h/rt	94
<i>n</i> -PrCO ₂ H	Br(CH ₂) ₃ Cl	3.3.1.B ¹ /20 h/rt	92
		3.3.1.B ² /20 h/rt	89
	<i>n</i> -C ₄ H ₉ Br	3.3.1.A/5 h/100°C	95
	PhCH ₂ I	3.3.1.H/10 min	68 ^f
<i>t</i> -BuCO ₂ H	CH ₂ Cl ₂	3.3.1.C/4 d/40°C	79
	PhCH ₂ I	3.3.1.H/10 min	72 ^f
	CH ₂ Cl ₂	3.3.1.C/4 d/40°C	80
<i>n</i> -C ₅ H ₁₁ CO ₂ H	CH ₂ =CHCH ₂ Br	3.3.1.H/3 min	52
	PhCH ₂ Br	3.3.1.H/10 min	72
Me(CH=CH) ₂ CO ₂ H	<i>n</i> -C ₄ H ₉ Br	3.3.1.A/5 h/100°C	90

^a B¹ uses TBA-Br, B² uses Aliquat. ^b 94% with 1 mmol of catalyst. ^c 99% when 0.16 g TiO₂ added. ^d 93% when 0.16 g TiO₂ added. ^e 92% with 1 mmol of catalyst. ^f Using TMBA-Cl.

aqueous NaOH (2M, 100 ml) is extracted with CH₂Cl₂ (3 × 250 ml). The combined extracts are dried (MgSO₄) and heated for 4 days. The solution is washed sequentially with H₂SO₄ (2.5 M, 2 × 300 ml), H₂O (300 ml), aqueous NaHCO₃ (sat. soln., 2 × 300 ml) and H₂O (300 ml), dried (MgSO₄), and evaporated to yield the methylene diester.

Method D (esterification of peptides and amino acids): Adogen (0.45 g, 1 mmol) and the alkylating agent (1.2 mmol) in CH₂Cl₂ is added at room temperature to the protected amino acid or peptide (1 mmol) in aqueous NaHCO₃ (sat. soln., 1 ml) and the mixture is stirred for up to 24 h. The mixture is extracted with CH₂Cl₂ (2 × 10 ml) and the extracts are washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the ester (e.g. benzyl esters of benzyloxycarbonyl protected amino acids >90%; dipeptides 70–90%).

Method E (t-butyl esters of peptides and amino acids): K₂CO₃ (36 g) is added to the amino acid (10 mmol) and TEBA-Cl (2.28 g, 10 mmol) in MeCONMe₂ (75 ml) at room temperature. Me₃CBr (65.75 g, 0.48 mol) is then added and the mixture is stirred at 55°C for 24 h. H₂O (1000 ml) is added to the cooled mixture and the precipitated material is collected and extracted with EtOAc (250 ml). The extract is washed with H₂O (2 × 100 ml), dried (Na₂SO₄), and evaporated to yield the *t*-butyl ester (80–100%)

Method F (from ethylene carbonates): Ethylene carbonate (2 g, 22 mmol), the carboxylic

acid (20 mmol) and TEA-I (0.93 g, 3.6 mmol) are heated at 150–155°C until the evolution of CO₂ ceases. EtOAc (100 ml) is added and the mixture is washed well with H₂O, dried (MgSO₄), and evaporated to yield the β -hydroxyethyl ester, RCO₂(CH₂)₂OH [e.g. R = Me, 74% (60 min); *n*-C₉H₁₉, 81% (35 min); 4-MeC₆H₄, 73% (60 min); 3,5-(O₂N)₂C₆H₃, 87% (30 min)].

Method G (supported catalysis): The potassium salt of the carboxylic acid (0.22 mol) and the alkylating agent (0.2 mol) are refluxed for 2 h with TMA-Cl on silica D22 (25%, 4.38 g, 10 mmol), prepared by stirring TMA-Cl (2.5 g) in MeOH (25 ml) with silica D22 (7.5 g) at room temperature for 1 h and then evaporating to dryness. The mixture is filtered and the solids are washed with CHCl₃ (4 \times 20 ml). The combined organic solutions are evaporated to yield the ester [e.g. HCO₂CH₂Ph, ~100%; HCO₂C₁₀H₂₁, 86% (in xylene at 120°C for 120 h); MeCO₂C₈H₁₇, 99% (in 2-ClC₆H₄Me at 150°C for 9 h)].

Method H (microwave reaction on carboxylic acid): The haloalkane (5 mmol), carboxylic acid (10 mmol) and TBBA-Cl (0.156 g, 0.5 mmol) are subjected to microwave irradiation in a sealed Pyrex tube for 10 min. The cooled reaction mixture is poured into H₂O (20 ml) and extracted with Et₂O (3 \times 10 ml). The extracts are washed with H₂O (10 ml) and aqueous NaHCO₃ (sat. soln, 2 \times 15 ml), dried (Na₂SO₄), and evaporated to yield the ester.

3.3.2 Esterification of aromatic acids

Method A: The finely powdered potassium salt of the carboxylic acid (11 mmol) is added to the alkylating agent [11 mmol for RX; 5.5 mmol for X(CH₂)_{*n*}X, 20 mmol with allylic and benzylic halides] and Aliquat or TBA-Br (0.1 mmol). The mixture is shaken vigorously for 15 min and then allowed to stand (see Table 3.9). The mixture is diluted with Et₂O (60 ml), filtered through Florisil, and evaporated to yield the ester.

Method B: The crushed acid (11 mmol), finely powdered KOH (1 equivalent for each CO₂H group), and Aliquat or TBA-Br (0.1 mmol) are shaken for 5 min* and then stirred with the alkylating agent (11 mmol for RX; 5.5 mmol for X(CH₂)_{*n*}X, 20 mmol with allylic and benzylic halides) (Table 3.9). The reaction is worked up as described in 3.3.2.A (*alternatively, the mixture can be heated at 140°C for 10 min and the caked residue finely powdered before the addition of the alkylating agent).

Method C (with microwave irradiation): The alkylating agent (10 mmol) and TBA-Br or Aliquat (1 mmol) are mixed with the potassium carboxylate (10 mmol) and then placed in a microwave oven (600 W) for 2–7 min. On completion of the reaction, CH₂Cl₂ (50 ml) is added. The crude mixture is filtered through Florisil and the filtrate is evaporated to yield the ester.

Method D (methylene diesters): See 3.3.1.C.

3.3.3 Resin-catalysed esterification of carboxylic acids (Table 3.10)

The quaternary ammonium resin (e.g. Amberlite® IRA-904) (2 mol equivalent) and the carboxylic acid (1 mol equivalent) are shaken in EtOH (25 ml) for *ca.* 30 min at room temperature. The resin is collected, washed with MeCN (2 \times 15 ml), and added to the alkylating agent (4 mol equivalent). The system is stirred at 20–25°C for 10–20 h and then filtered. Fractional distillation of the filtrate yields the ester.

TABLE 3.9
Selected examples of the phase-transfer catalysed formation of aromatic esters

Acid	Alkylating agent	Reaction conditions	% yield
PhCO ₂ H	EtBr	3.3.2.A/B/14 h/38 °C	96
	PhCH ₂ Br	3.3.2.A/B/8 h/rt	92
	<i>n</i> -C ₈ H ₁₇ Br	3.3.2.A/B/2 h/85 °C	92
		3.3.2.C/2.5 min/150 °C	99
	<i>n</i> -C ₁₆ H ₃₃ Br	3.3.2.A/B/24 h/50 °C	90
	<i>i</i> -PrBr	3.3.2.A/B/24 h/60 °C	91
	cyclo-C ₆ H ₁₃ Br	3.3.2.A/B/24 h/85 °C	20
	C ₆ H ₁₃ CHBrMe	3.3.2.A/B/24 h/85 °C	76
	CH ₂ Cl ₂	3.3.2.D/4 d/40 °C	88
	Br(CH ₂) ₄ Br	3.3.2.A/B/1 h/85 °C	84
	Br(CH ₂) ₁₂ Br	3.3.2.A/B/24 h/85 °C	88
4-Me ₂ NC ₆ H ₄ CO ₂ H	<i>n</i> -C ₈ H ₁₇ Br	3.3.2.C/3 min/202 °C	97
4-MeOC ₆ H ₄ CO ₂ H	<i>n</i> -C ₈ H ₁₇ Br	3.3.2.C/2 min/174 °C	82
	CH ₂ Cl ₂	3.3.2.D/4 d/40 °C	85
4-CNC ₆ H ₄ CO ₂ H	<i>n</i> -C ₈ H ₁₇ Br	3.3.2.C/3 min/>170 °C	80
4-O ₂ NC ₆ H ₄ CO ₂ H	(MeO) ₂ SO ₂	3.3.2.A/24 h/rt	91
	PhCH ₂ Br	3.3.2.A/8 h/rt	93
	<i>n</i> -C ₈ H ₁₇ Br	3.3.2.A/3 h/85 °C	92
		3.3.2.C/2 min/202 °C	81
	<i>n</i> -C ₁₆ H ₃₃ Br	3.3.2.A/40 h/85 °C	93
	CH ₂ Cl ₂	3.3.2.D/4 d/72 °C	60 ^a
2,4,6-Me ₃ C ₆ H ₂ CO ₂ H	MeI	3.3.2.B/2 h/85 °C	98
	EtBr	3.3.2.B/2 h/85 °C	98
	<i>n</i> -C ₁₆ H ₃₃ Br	3.3.2.B/8 h/85 °C	88
2-O ₂ NC ₆ H ₄ CO ₂ H	PhCH ₂ Br	3.3.2.A/8 h/rt	89
	<i>n</i> -C ₈ H ₁₇ Br	3.3.2.A/3 h/85 °C	94
	<i>n</i> -C ₁₆ H ₃₃ Br	3.3.2.A/40 h/85 °C	91
C ₆ H ₃ -1,2,4-(CO ₂ H) ₃	(EtO) ₂ SO ₂	3.3.2.A/24 h/60 °C	77
	CH ₂ =CHCH ₂ Br	3.3.2.A/16 h/60 °C	88
	PhCH ₂ Br	3.3.2.A/16 h/60 °C	88
C ₆ H ₄ -1,3-(CO ₂ H) ₂	(EtO) ₂ SO ₂	3.3.2.A/60 h/60 °C	4
	PhCH ₂ Br	3.3.2.A/85 h/60 °C	20
2-Furoic acid	(EtO) ₂ SO ₂	3.3.2.A/13 h/60 °C	81
	PhCH ₂ Br	3.3.2.A/15 h/rt	91
	<i>n</i> -C ₈ H ₁₇ Br	3.3.2.A/24 h/85 °C	88
Pyrrole-2-CO ₂ H	(EtO) ₂ SO ₂	3.3.2.B/24 h/rt	87
	PhCH ₂ Br	3.3.2.B/24 h/rt	87
Pyridine-2-CO ₂ H	(EtO) ₂ SO ₂	3.3.2.B/24 h/rt	49
Pyridine-3-CO ₂ H	(EtO) ₂ SO ₂	3.3.2.B/43 h/rt	82
Pyridine-4-CO ₂ H	(EtO) ₂ SO ₂	3.3.2.B/43 h/rt	87

^a PhMe (800 ml) added to the reaction mixture; monochloromethyl ester also obtained. The yield decreases with increased reaction time.

The reaction of (dibromomethyl)arenes with sodium acetate and calcium carbonate under liquid:liquid conditions yields not the bisacetoxo derivative but the aldehyde in high yield (65–82%) [29, 30].

TABLE 3.10
Selected examples of resin-catalysed esterification

Acid	Alkylating agent	Reaction conditions	% yield
<i>n</i> -C ₁₁ H ₂₃ CO ₂ H	MeI	3.3.3/4 h	93 ^a
	<i>i</i> -PrBr	3.3.3/6 h	52 ^{a,b}
cyclo-C ₆ H ₁₁ CO ₂ H	MeI	3.3.3/16 h	76 ^a
	<i>i</i> -PrBr	3.3.3/14 h	28 ^{a,b}
PhCO ₂ H	MeI	3.3.3/2 h	90 ^a
	MeOTos	3.3.3/17 h	91 ^a
	PhCH ₂ Cl	3.3.3/6 h	73 ^b
	<i>i</i> -PrBr	3.3.3/13 h	60 ^{a,b}
	BrCH ₂ CO ₂ Et	3.3.3/5 h	99 ^c
PhCH=CHCO ₂ H	MeI	3.3.3/21 h	97 ^a
	<i>i</i> -PrBr	3.3.3/14 h	59 ^{a,b}
2-Furoic acid	MeI	3.3.3/10 h	94
	EtI	3.3.3/10 h	92
	<i>n</i> -BuI	3.3.3/10 h	92
	2-furylCH ₂ Br	3.3.3/10 h	78
2-FurylCH=CHCO ₂ H	MeI	3.3.3/12 h	99
	EtI	3.3.3/12 h	99
5-Nitro-2-furoic acid	2-furylCH ₂ Br	3.3.3/12 h	80

^a in *n*-C₆H₁₄. ^b at 50°C. ^c in Et₂O.

3.3.4 Solvolysis of (dibromomethyl)arenes

The (dibromomethyl)arene (1 mmol) is heated under reflux with NaOAc (0.35 g), CaCO₃ (0.215 g) and TBA-Br (75 mg, 0.23 mmol) in H₂O (5 ml). The mixture is filtered and the filtrate is made neutral by the addition of dilute HCl. The aqueous solution is extracted with CH₂Cl₂ (3 × 15 ml) and the dried (MgSO₄) extracts are evaporated to yield the aldehyde.

Methyl esters undergo trans-esterification with the quaternary ammonium salts at high temperature and the reaction has been used with some effect for the preparation of, for example, *n*-butyl esters by heating the methyl ester with tetra-*n*-butylammonium chloride at 140°C [31]. Optimum yields (>75%) are obtained in HMPA or in the absence of a solvent. A two-step (one-pot) trans-esterification under phase-transfer catalysed conditions in which the carboxylate anion generated by initially hydrolysis of the ester is alkylated has been reported for Schiff's bases of α-amino acids [32] and for *N*-alkoxycarbonylmethyl β-lactams [33]. Direct trans-esterification of methyl and ethyl esters with alcohols under basic catalytic conditions occurs in good yield in the presence of Aliquat [34, 35].

3.3.5 Trans-esterification under phase-transfer catalysed conditions

Method A: The methyl carboxylic ester (12.9 mmol) in CH₂Cl₂ (25 ml) is added to TBA-Br (0.62 g, 1.9 mmol) and aqueous NaOH (5M, 4.7 ml) and the mixture is stirred

vigorously for *ca.* 2 h until the hydrolysis is complete, as shown by HPLC analysis. The pH of the solution is adjusted to 7.3 by the addition of aqueous HCl (5 M). The alkylating agent is added (13.9 mmol) and the mixture is stirred at room temperature for *ca.* 12 h. The organic phase is then separated, washed with aqueous HCl (1 M, 2 × 20 ml), aqueous NaHCO₃ (5%, 25 ml), dried (MgSO₄) and evaporated to yield the ester.

Method B: The methyl ester (10 mmol), alcohol (10 mmol), K₂CO₃ (5 mmol) and Aliquat (0.2 g, 0.5 mmol) are stirred in a closed evacuated vessel at 20 mm pressure for 8–24 h. The ester is isolated from the filtered mixture by distillation (75–100%).

Trans-esterification of ethylene carbonates (**3.3.1.F**) produces β -hydroxyethyl esters in good yield (>70%), when the reaction is catalysed by tetraethylammonium halides [36].

Phase-transfer catalysis succeeds where the classical method fails in the synthesis of *cis*-3,5-diacetoxycyclopentene, which is a key compound in prostaglandin synthesis. In contrast with the formation of a mixture of the *cis* and *trans*-diesters and the 3,4-diacetoxy derivative, *cis*-3,5-diacetoxycyclopentene is obtained >90% purity from the 3,5-dibromo derivative, when treated with potassium acetate in the presence of a quaternary ammonium salt [4].

3.3.6 *cis*-3,5-Diacetoxycyclopentene

cis-3,5-Dibromocyclopentene (2.0 g, 9 mmol) in CCl₄ (5 ml) is added to MeCO₂K (3.0 g, 31 mmol) and TOPA-Cl (0.7 g, 2 mmol) in H₂O (2 ml) over a period of 2.5 h at 42°C.* The mixture is stirred for a further 2.5 h; Et₂O (50 ml) and H₂O (10 ml) is then added. The organic phase is separated, and the aqueous phase is extracted with Et₂O (20 ml). The dried (Na₂SO₄) organic solutions are evaporated to yield the diacetoxy derivative (97%) (* at 60°C a mixture of 3,5- (95%) and 3,4-diacetoxycyclopentene (5%) is obtained).

A complex reaction between perfluoro 2-methylpent-2-ene and carboxylic acids in the presence of potassium carbonate and Aliquat produces the acid fluoride, as the major product, with variable amounts of the 3-acyloxy perfluorinated alkene [37]. The procedure has little value for the synthesis of either compound.

The reaction of acid chlorides or anhydrides with alcohols or phenols is catalysed by the addition of a quaternary ammonium salt [38]. Again, primary and secondary alcohols are more readily acylated. Tertiary alcohols tend to undergo elimination reactions and require the addition of anhydrous sodium carbonate to moderate this reaction. It was not possible to prepare tertiary alkyl benzoates by this procedure. Although more vigorous conditions or prolonged reaction times may be required, acylation of sterically crowded phenols is possible and yields are good [39]. Cyclic esters have been obtained from diols with diacid chlorides [40] and macrocyclic ionophoric pyridino-crown ethers have been synthesized in good yield (>70%) from the fluoride-catalysed reaction of oligo(ethylene)glycols with pyridine-2,6-bis(carbonylchloride) [41].

Catalysed selective benzoylation of benzylideneglycosides has been reported [42]. Unlike the Schotten–Bauman reaction using acid chlorides in the presence of

pyridine, where intramolecular H-bonding of the reactive hydroxyl groups enhances the rate of acylation, it has been found that H-bonding under phase-transfer catalytic conditions appears to diminish the activity of the hydroxyl groups [43]. Silyl ethers and sterically hindered hydroxyl groups of nucleosides react readily under the influence of tetra-*n*-butylammonium fluoride with anhydrides in high yield (98–100%) at room temperature [44].

3.3.7 Catalysed reaction of acid chlorides and anhydrides with alcohols and phenols (Table 3.11)

Method A with primary and secondary alcohols: The alcohol (0.1 mol) and TBA-Cl (2.88 g, 10 mmol) in CH_2Cl_2 or CCl_4 (50 ml) is stirred with aqueous NaOH (30%, 50 ml) at 0°C for *ca.* 5 min before the addition of the acid chloride (0.14 mol) or anhydride (0.12 mol) in CH_2Cl_2 (20 ml). The mixture is stirred vigorously for 5–10 min and the organic phase is then separated, washed with H_2O until neutral, dried (CaSO_4), and fractionally distilled to yield the ester.

Method B with tertiary alcohols: Anhydrous Na_2CO_3 (30 g) is added to the alcohol (0.1 mol) and TEBA-Cl (2.3 g, 10 mmol) in CH_2Cl_2 (50 ml), followed by the acid chloride (0.1 mol). The stirred mixture is refluxed for *ca.* 3 h and then filtered. The residue is extracted with CH_2Cl_2 (10 ml) and the combined organic solution is washed well with H_2O until neutral, dried (CaSO_4), and fractionally distilled.

Method C with phenols: The acid chloride (12 mmol) in CH_2Cl_2 (5 ml) is added dropwise to the phenol (10 mmol), TBA-Br (12 mg, 0.04 mmol), and NaOH (1 g, 25 mmol) in

TABLE 3.11
Phase-transfer catalysed esterification of alcohols and phenols with
acid chlorides

Acid chloride	Alcohol/phenol	% yield
MeCOCl	<i>n</i> -C ₃ H ₇ CH ₂ OH	89
	<i>i</i> -C ₃ H ₇ CH ₂ OH	72
	CH ₂ =CHCH ₂ OH	69
	PhCH ₂ OH	80
	PhMeCHOH	61
	PhCMe ₂ OH	79
	EtCMe ₂ OH	80
	2,6-(<i>t</i> -Bu) ₂ -4-MeC ₆ H ₂ OH	72 ^a
EtCOCl	CH ₂ =CHCH ₂ OH	69
	Me ₃ COH	84
	EtCMe ₂ OH	78
	2,6-(<i>t</i> -Bu) ₂ -4-MeC ₆ H ₂ OH	76 ^a
	Me ₃ COH	75
PhCH ₂ COCl	Me ₃ COH	75
PhCOCl	<i>n</i> -C ₃ H ₇ CH ₂ OH	90
	<i>i</i> -C ₃ H ₇ CH ₂ OH	91
	CH ₂ =CHCH ₂ OH	70
	PhCH ₂ OH	85
	PhMeCHOH	65

^a 120 h reaction time.

CH_2Cl_2 (25 ml) over a period of *ca.* 30 min. The mixture is stirred for 120 h (for sterically hindered phenols), filtered, and evaporated to yield the phenyl ester.

Method D with oligo(ethylene)glycols: Pyridine-2,6-bis(carbonyl chloride) (2 g, 10 mmol) is added at room temperature over 30 min to a stirred mixture of TEBA-Cl (0.11 g, 0.5 mmol), KF (1.16 g, 20 mmol), and the oligo(ethylene)glycol (10 mmol) in CH_2Cl_2 . The mixture is stirred for a further 3 h until the reaction is complete, as shown by TLC, then filtered and the solid is washed well with CH_2Cl_2 . The organic solutions are evaporated to yield the macrocycle [e.g. with $\text{HO}[(\text{CH}_2)_2\text{O}]_n\text{H}$, $n = 3$, 90%; $n = 4$, 74%]

In what appears, initially, to be a closely similar reaction, acid chlorides react with alkyl halides under solid:liquid two-phase conditions using sodium hydrogen carbonate in the presence of sodium iodide and tetra-*n*-butylammonium bromide [45]. Although the mechanism is not clear, it has been proposed that the acid chloride is initially converted into the carboxylate anion. It is also probable that the halogen interchange between the sodium iodide and the alkyl halides enhances their reactivity. Although the yields are high, the availability of the alkyl halides and alcohols are usually similar and there appears to be little to commend this process over the catalysed reaction of the acid chlorides with the alcohols.

3.3.8 Esters from acid chlorides and alkyl halides

The acid chloride (10.8 mmol) and the alkyl halide (11.1 mmol) are heated at *ca.* 80°C for 5–8 h with anhydrous NaHCO_3 or KHCO_3 (29.8 mmol), NaI (0.19 g) and TBA-Br (0.38 g, 1.2 mmol) in MeCN (30 ml). The mixture is filtered and the filtrate evaporated under reduced pressure to yield the esters (Table 3.12).

1-Acyloxy-1-cyanoalkanes [45, 46], which can be used as precursors for ketones [47], α -hydroxy ketones [48] and 1,4-dicarbonyl compounds [47], are prepared in one pot from the appropriate aldehyde, sodium or potassium cyanide, and the acylating agent under phase-transfer catalytic conditions [47–49]. Attempts to synthesize chiral cyanhydrins using chiral phase-transfer catalysts have been unsuccessful (see Section 12.3).

TABLE 3.12
Aromatic esters from acid chlorides and alkyl halides

Acid chloride	Alkyl halide	Reaction conditions	% yield
$4\text{-O}_2\text{NC}_6\text{H}_4\text{COCl}$	<i>n</i> -BuCl	3.3.8/8 h/80°C	83
$4\text{-O}_2\text{NC}_6\text{H}_4\text{COCl}$	PhCH_2Cl	3.3.8/8 h/80°C	98
$4\text{-O}_2\text{NC}_6\text{H}_4\text{COCl}$	$3\text{-BrC}_6\text{H}_4\text{CH}_2\text{Cl}$	3.3.8/8 h/80°C	93
$4\text{-O}_2\text{NC}_6\text{H}_4\text{COCl}$	$4\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{Cl}$	3.3.8/8 h/80°C	90
$2\text{-ClC}_6\text{H}_4\text{COCl}$	$4\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{Cl}$	3.3.8/8 h/80°C	57
PhCH_2COCl	$4\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{Cl}$	3.3.8/8 h/80°C	60
PhCH_2COCl	2-naphthyl CH_2Cl	3.3.8/7 h/80°C	55

3.3.9 1-Acyloxy-1-cyanoalkanes (Table 3.13)

Method A (carbonates): The aryl aldehyde (0.1 mol) in CH_2Cl_2 (75 ml) and alkyl chloroformate (0.3 mol) are added to KCN (13.2 g) and TEBA-Cl (0.23 g, 1 mmol) in H_2O (100 ml) over 10 min at 0°C . The mixture is stirred at 10°C for 2.5 h and the organic phase is then separated, washed with H_2O (2×30 ml), dried (K_2CO_3), and evaporated under vacuum to yield the cyanhydrin carbonate.

Method B (benzoates): The aldehyde (0.1 mol) in CH_2Cl_2 (100 ml) is added at 0.5°C to NaCN (19.6 g, 0.4 mol) and TMBA-Cl (3.0 g, 13 mmol) in H_2O (75 ml). The mixture is stirred for 10 min and PhCOCl (14 g, 0.1 mol) in CH_2Cl_2 (50 ml) is added over a period of 30 min. The organic phase is separated, washed with aqueous Na_2CO_3 (3×30 ml), H_2O (30 ml), brine (30 ml) and H_2O (30 ml), dried (MgSO_4), and evaporated to yield the benzoate.

TABLE 3.13
One-pot synthesis of 1-acyloxy-1-cyanoalkanes

Aldehyde	Acylating agent	Method	% yield
PhCHO	ClCO_2Et	3.3.9.A	83
4- $\text{O}_2\text{NC}_6\text{H}_4\text{CHO}$	ClCO_2Et	3.3.9.A	44
4- $\text{MeOC}_6\text{H}_4\text{CHO}$	ClCO_2Et	3.3.9.A	36
4- $\text{PhOC}_6\text{H}_4\text{CHO}$	ClCO_2Et	3.3.9.A	92
2,4- $\text{Cl}_2\text{C}_6\text{H}_3\text{CHO}$	ClCO_2Et	3.3.9.A	93
2-furylCHO	ClCO_2Et	3.3.9.A	100
<i>n</i> - $\text{C}_6\text{H}_{13}\text{CHO}$	ClCO_2Et	3.3.9.A	100
6-PhO-2-pyridylCHO	ClCO_2Et	3.3.9.A	92
4-PyridylCHO	PhCOCl	3.3.9.B	40

An interesting preparation of alkyl carboxylates in high yield (Table 3.14) from the sodium salt of the carboxylic acids under mild phase-transfer catalytic conditions involves their reaction with alkyl chlorosulphate [50] and has been used with success in the preparation of alkyl esters derived from β -lactam antibiotics. The procedure is also excellent for the production of chloromethyl esters, particularly where the carboxylic acids will not withstand the 'classical' Lewis acid-catalysed procedure using an acid chloride and formaldehyde, or where the use of iodochloromethane [51] results in the formation of the bis(acyloxy)methane. The procedure has been applied with some success to the synthesis of chloromethyl *N*-protected α -amino carboxylates [52].

A one-pot conversion of carboxylic acids into esters and amide derivatives from alcohols, amines or hydrazines has been reported [53], which involves the initial reaction of the acid with methane- or toluenesulphonyl chloride to yield a mixed anhydride.

TABLE 3.14

Selected examples of the preparation of carboxylic esters using chlorosulphates

RCOOH	R ¹ OSO ₂ Cl	% yield of RCOOR ¹
R = Ph	R ¹ = CH ₂ Cl	80
	<i>n</i> -Bu	86
	CH ₂ SO ₂ Cl	73 ^a
Me(CH ₂) ₄	CH ₂ Cl	73
	CH ₂ SO ₂ Cl	79 ^a
Me(CH ₂) ₆	CH ₂ Cl	80
<i>t</i> -Bu	CH ₂ Cl	64
Cl(CH ₂) ₄	Et	80
BocNHCH ₂	CH ₂ Cl	87
BocNHCHMe	CH ₂ Cl	94
BocNHCH(CO ₂ <i>t</i> -Bu)(CH ₂) ₂	CH ₂ Cl	98
BocNH(CH ₂) ₅	CH ₂ Cl	91
BocNMe(CH ₂) ₂	CH ₂ Cl	93
BocNHCH(<i>i</i> -Pr)CONH(CH ₂) ₂	CH ₂ Cl	79

^a (RCO₂)₂CH₂.

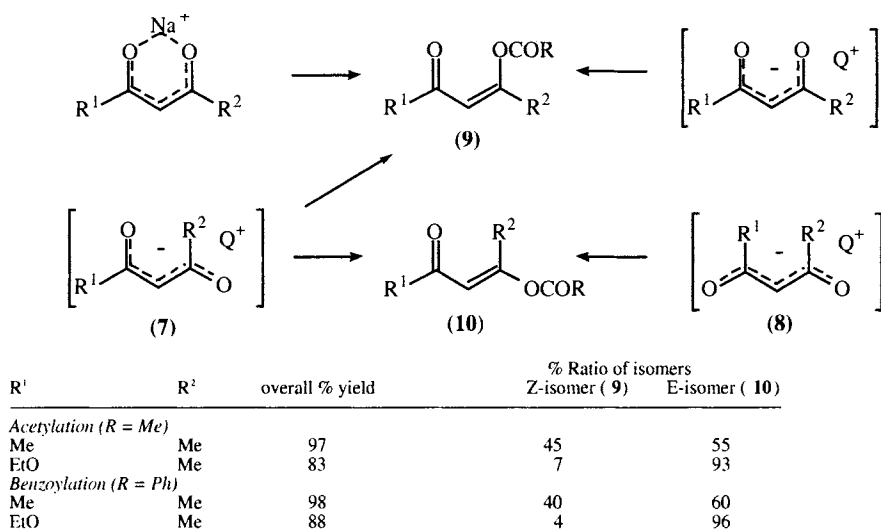
3.3.10 Esterification using chlorosulphates

The carboxylic acid (0.2 mol), NaHCO₃ (63.8 g, 0.76 mol) and TBA-HSO₄ (6.8 g, 0.02 mol) in a 1 : 1 two-phase H₂O:CH₂Cl₂ system (400 ml) are stirred at *ca.* 20°C. The chlorosulphate (0.23 mol) in CH₂Cl₂ (50 ml) is added slowly such that the reaction mixture temperature is <30°C. The mixture is stirred for a further 30 min, before the organic phase is separated, dried (MgSO₄), and evaporated to yield the ester.

3.3.11 One-pot conversion of carboxylic acids into esters and amides

The acid (10 mmol), MeSO₂Cl or TosCl (10 mmol), anhydrous K₂CO₃ (5.5 g), TEBA-Cl (0.23 g, 1 mmol) in PhH (60 ml) are stirred under reflux for *ca.* 40 min: (a) the amine (or hydrazine) (10 mmol) is added and the mixture stirred for a further 10 min under reflux. The filtered mixture is evaporated and the residue recrystallized to yield the amide (or hydrazide) (e.g. PhCH=CHCONHPh, 94%; PhCONHNHCH₂CO₂Et, 82%); or (b) addition of the alcohol (10 mmol) instead of the amine, and further reflux for 40–90 min, followed by filtration of the cooled mixture and fractional distillation yields the ester (e.g. PhCO₂Ph, 89%; PhCO₂(CH₂)₂NMe₂, 92%).

The preferential *E*-configuration of the enol esters, derived from β-dicarbonyl compounds under phase-transfer conditions, contrasts with the formation of the *Z*-enol esters when the reaction is carried out by classical procedures using alkali metal alkoxides. In the latter case, the ‘U’ form of the intermediate enolate anion is stabilized by chelation with the alkali metal cation, thereby promoting the exclusive formation of the *Z*-enol ester (9) (Scheme 3.5), whereas the formation of the ion-pair with the quaternary ammonium cation allows the carbanion to adopt the thermodynamically more stable ‘sickle’ or ‘W’ forms, (7) and (8), which lead to the *E*-enol esters (10) [54].



Scheme 3.5

3.3.12 Acetylation and benzoylation of β -dicarbonyl compounds

The β -dicarbonyl compound (10 mmol) in CH_2Cl_2 is added, with stirring, to TBA- HSO_4 (3.4 g, 10 mmol) in aqueous NaOH (2M, 10 ml) at 20°C . The acid chloride (10 mmol) is added dropwise over *ca.* 2 min and the mixture is stirred for a further 1 h. The aqueous phase is separated, extracted with CH_2Cl_2 (10 ml), and the combined organic solutions are washed with H_2O (2×10 ml), dried (MgSO_4), and evaporated. Et_2O (25 ml) is added to the residue, the solution is filtered, and evaporated to yield the enol esters.

The phase-transfer catalysed reaction of alkyl halides with potassium carbonate in dimethylacetamide, or a potassium carbonate/potassium hydrogen carbonate mixture in toluene, provides an excellent route to dialkyl carbonates without recourse to the use of phosgene [55, 56]. An analogous reaction of acid chlorides with sodium hydrogen carbonate in benzene, or acetonitrile, produces anhydrides (3.3.29.B, >80%), although there is a tendency in acetonitrile for aliphatic acid chlorides to hydrolyse yielding the acids [57].

Symmetrical and unsymmetrical carbonates have also been obtained from the reaction of chloroformates with alcohols under solid:liquid conditions [55], and the reaction of carbamoyl fluorides with alcohols produces alkyl carbamates [58]. *t*-Butyloxycarbonylation of alcohols and phenols is effected by trans-esterification of di-*t*-butyl carbonate under basic phase-transfer catalysed conditions [59]. Yields tend to be high for the reaction with the phenols (>85%), but only moderate with the alcohols (30–81%).

3.3.13 Dialkyl carbonates

Method A: Freshly dried K_2CO_3 (5 g, 50 mmol), the alkyl halide (16.6 mmol) and TBA-Br (0.336 g, 5 mmol) in dry MeCONMe₂ (20 ml) are stirred at 115 – 125°C for 2–3 h.

When the reaction is complete, as shown by GLC analysis, the mixture is cooled to room temperature, filtered, and H₂O (50 ml) is added. The organic phase is separated, dried (CaSO₄), and fractionally distilled to yield the carbonate [e.g. (PhCH₂O)₂CO, 61%; (MeO)₂CO, 63%; (4-MeC₆H₄CH₂O)₂CO, 88%].

Method B: The alkylating agent (0.1 mol) and Aliquat (0.4 g, 1 mmol) in PhMe (10 ml) are added to an intimate anhydrous mixture of KHCO₃ (10 g) and K₂CO₃ (14 g) and the mixture is heated at 100°C for 8–15 h. On completion of the reaction, the mixture is filtered and the filtrate fractionated to yield the carbonate [e.g. (*n*-C₃H₁₁O)₂CO, 72%; (*n*-C₁₅H₃₁O)₂CO, 83%; (PhO)₂CO, 85%; (2-MeC₆H₄O)₂CO, 86%].

Method C from chloroformates: The chloroformate (40 mmol) in PhMe (20 ml) is added dropwise to K₂CO₃ (7 g), the alcohol (10 mmol) and Adogen (0.4 g, 1 mmol) in PhMe (5 ml) and the mixture is stirred at 100°C for 6 h. Et₂O (50 ml) is added. The mixture is filtered and fractionally distilled to yield the carbonate [e.g. ClCO₂CH₂Ph with *n*-C₆H₁₃OH yields PhCH₂OH (6%), (PhCH₂O)₂CO (27%), and *n*-C₆H₁₃OCO₂CH₂Ph (67%)].

3.3.14 *t*-Butyloxycarbonylation of alcohols and phenols

Aqueous NaOH (30%, 3.7 ml) is added at 0°C to the alcohol or phenol (7.45 mmol), TBA-HSO₄ (73 mg, 0.22 mmol), and (*t*-BuO)₂CO (1.94 g, 8.89 mmol) in CH₂Cl₂ (2 ml) and the mixture is stirred vigorously until TLC analysis shows the reaction to be complete. CH₂Cl₂ (15 ml) is added and the organic phase is separated, washed well with brine, dried (MgSO₄), and evaporated to yield the unsymmetrical carbonate (e.g. from PhOH, 89%; 4-MeOC₆H₄OH, 84%; 4-MeCOC₆H₄OH, 94%; PhCH=CHCH₂OH, 93; CH₂=CHCH₂OH, 81%; cyclo-C₆H₁₁OH, 30%; *n*-C₁₂H₂₅OH, 52%).

The reaction of silyl enol ethers with fluoroformates and fluoroformamides, catalysed by the addition of tetra-*n*-butylammonium fluoride, produces enol carbonates and carbamates in acceptable yields [60].

3.3.15 Carbamates from alcohols

The carbamoyl fluoride (8.47 mmol) in PhMe (5 ml) is added to the alcohol (8.47 mmol), NaOH (0.51 g, 12.71 mmol) and TBA-HSO₄ or THA-Cl (0.85 mmol) in PhMe (5 ml) and H₂O (10 ml). The two-phase system is stirred until the reaction is complete, as shown by GLC analysis. The mixture is poured into PhMe (10 ml) and H₂O (10 ml) and the organic phase is separated, washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the carbamate.

3.3.16 Enol carbonates and carbamates from oxysilanes

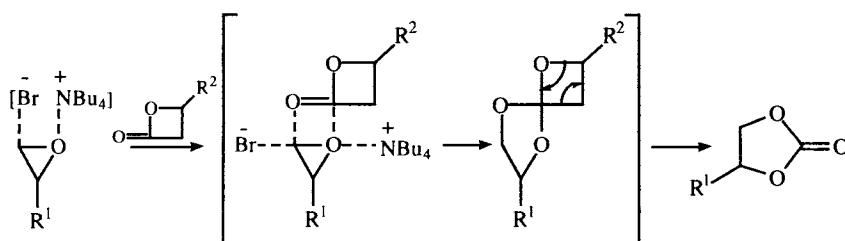
The enol silane (1 mol) and TBA-F (18.3 g, 70 mmol) in THF (50 ml) are stirred with the fluoroformate or fluoroformamide (1.3 mol) (see Table 3.15). The mixture is filtered and fractionally distilled to yield the carbonate or carbamate.

Cyclic carbonates have been prepared in the regiospecific ring-opening of oxiranes by butyrolactones catalysed by the quaternary ammonium salt (Scheme 3.6)

TABLE 3.15
Selected examples of enol carbonates and carbamates

		Reaction conditions	% yield
<i>Enol carbonates from FCO₂R and Me₃SiOR¹</i>			
R = <i>i</i> -Bu	R ¹ = CH ₂ =CH	3.3.16/3 h/0°C	71
<i>n</i> -Bu	CH ₂ =CMe	3.3.16/20 min/25°C	73
Ph	CH ₂ =CMe	3.3.16/23 h/65°C	65
cyclo-C ₆ H ₁₁	but-1,3-dien-2-yl	3.3.16/30 min/25°C	79
<i>i</i> -Bu	1-cyclo-C ₃ H ₇ C=CH ₂	3.3.16/30 min/25°C	93
cyclo-C ₆ H ₁₁	cyclohex-1-en-1-yl	3.3.16/9 h/25°C	78
<i>i</i> -Pr	3,4-dihydronaphth-1-yl	3.3.16/1 h/25°C	53
<i>Enol carbamates from FCONR₂ and Me₃SiOR¹</i>			
R = (CH ₂) ₂ O(CH ₂) ₂	R ¹ = buta-1,3-dien-2-yl	3.3.16/51 h/25°C	52
Me	3,4-dihydronaphth-1-yl	3.3.16/20 h/50°C	90

[61]. Yields are variable, but the reaction appears to be promoted by the presence of alkoxymethyl substituents on the oxirane ring. Reactions with β -propiolactones give lower yields (<10%). Cyclic carbonates can also be obtained from the zinc(II) promoted reaction of oxiranes with carbon dioxide [62]; the stereochemistry of substituents on the oxirane are retained in the carbonate.



Scheme 3.6

3.3.17 Cyclic carbonates

Method A: The β -butyrolactone (50 mmol) in PhMe (10 ml) is added to the oxirane (50 mmol) and TBA-Br (1.7 g, 5 mmol) and the mixture is stirred at 100°C under N₂. On completion of the reaction (*ca.* 15 h), PhH (100 ml) is added and the organic phase is washed with H₂O (3 \times 10 ml), dried (MgSO₄), and poured into *n*-C₆H₁₄ (500 ml). The lactone precipitates from solution and can be collected by filtration (R¹ = PhOCH₂, 87%; MeOCH₂, 74%; *n*-BuOCH₂, 56%; CH₂=CHCH₂OCH₂, 46%; Ph, 36%; CH₂Cl, 44%).

Method B: CO₂ is passed through a mixture of the oxirane (20 mmol), TBA-I (60 mg, 0.16 mmol), and ZnCl₂ (50 mg, 0.04 mmol) at room temperature. The cyclic carbonate is isolated by fractional distillation (e.g. 52% from oxirane; 98% from methyloxirane; 17% from phenyloxirane).

Cyclic thionocarbonates are formed under solid:liquid phase-transfer catalysed conditions from the reaction of diols with carbon disulphide [63]. The reaction has been specifically described for the reaction of carbohydrates, but should be generally applicable to all diols.

3.3.18 Cyclic thionocarbonates

Powdered KOH (0.38 g) is added to the diol (1 mmol) and TBA-HSO₄ (0.34 g, 1 mmol) in CH₂Cl₂ (15 ml) at 10°C with stirring. After 5 min, CS₂ (83 mg) is added, followed, after a further 15 min, by MeI (0.17 g). The reaction mixture is stirred at room temperature for 15 min and CH₂Cl₂ (15 ml) is then added and the mixture is washed with H₂O (5 × 20 ml). The dried (MgSO₄) organic phase is evaporated to yield the thionocarbonate.

Hydrolysis of formate esters, which are produced by the solid:liquid two-phase reaction of haloalkanes with sodium formate [64] or via the use of a triphase catalytic system [65], has been shown to be a more effective route to the alcohols, compared with the simple nucleophilic displacement of the halogen by the hydroxyl group which can lead to the formation of symmetrical ethers. Using procedure 3.3.19.B, α,ω -dichloroalkanes produce diesters, which can be hydrolysed to diols [64], whereas the corresponding reaction under strongly basic conditions produces cyclic ethers, presumably via the initial formation of ω -chloroalkyl formates [64]. A similar reaction between the haloalkanes and hydrogen carbonate anion leads directly to the alcohols. Resin-supported carbonate ions convert haloalkanes directly into the alcohols [65,66] with the expected order of reactivity I>Br>Cl, whereas secondary haloalkanes tend to undergo an elimination reaction [66].

3.3.19 Alkyl formates and alkanols

Method A: The bromoalkane (0.39 mol) is refluxed in Me₂CO (30 ml) with Amberlyst A-23 resin (in HCO₂⁻ form) (3.87 g equivalent to 3.65 mmol formate per g) for 72 h. The mixture is filtered and the filtrate is evaporated to yield the formate ester, HCO₂R (e.g. R = *n*-Bu 46%; *n*-C₈H₁₇ 76%; PhCH=CHCH₂ 92%; PhCH₂ ~100%), which upon stirring with aqueous HCl (3M, 1 ml) at 20°C for 15 min yields the corresponding alkanol.

Method B: The chloroalkane or α,ω -dichloroalkane (0.1 mol) and HCO₂Na (13.6 g, 0.2 mol for the chloroalkane, 27.2 g, 0.4 mol for the α,ω -dichloroalkane) are stirred with TBA-Br (1.61 g, 5 mmol) until the reaction is complete (Table 3.16). H₂O (10 ml) is added to the cooled mixture. The organic phase is separated, dried (MgSO₄), and fractionally distilled to yield the formate ester. When aqueous NaOH (50%, 4.5 ml) is added dropwise over 30 min to the vigorously stirred reaction mixture, the alcohol (diol) is formed, which can be isolated by extraction from the reaction mixture with butanone (2 × 20 ml) and fractional distillation.

Method C: Amberlyst A-23 (in CO₃²⁻ form) (11 g) and the bromoalkane (11 mmol) are stirred vigorously in refluxing PhH (20 ml) until all the bromoalkane is consumed. The filtered solution is evaporated to yield the alkanol [e.g. *n*-C₈H₁₇OH, 90% (7 h); PhCH₂OH, 91% (2 h); Me₂C=CHCH₂OH, 95% (1 h); 1,2-(HOCH₂)C₆H₄, 85% (2 h)].

TABLE 3.16
Selected examples of alkyl formates, alkanols and diols

Haloalkane	Reaction conditions	% yield ester	% yield alkanol or diol
PhCH ₂ Cl	3.3.19.B/120°C/2 h	94	94
<i>n</i> -C ₈ H ₁₇ Cl	3.3.19.B/125°C/1.5 h	95	96
Cl(CH ₂) ₃ Cl	3.3.19.B/115°C/1.5 h	96	94
ClCH ₂ CH=CHCH ₂ Cl	3.3.19.B/70°C/3 h	97	91

3.3.20 Cyclic ethers via formate esters from α,ω -dichloroalkanes

The α,ω -dichloroalkane (0.1 mol), HCO₂N_a (3 g, 50 mmol), Aliquat (0.8 g, 2 mmol) and powdered KOH (16.8 g) are stirred at 80–150°C for 10 min in an apparatus set up with a fractionating column for continuous distillation. The cyclic ether is collected by distillation as it is formed [e.g. 70% oxirane from Cl(CH₂)₂Cl; 95% tetrahydrofuran from Cl(CH₂)₄Cl; 80% tetrahydropyran from Cl(CH₂)₅Cl; 30% oxepane from Cl(CH₂)₆Cl].

Phase-transfer catalysis can be used to mimic high dilution reaction conditions and has been utilized to good effect in the synthesis of large ring lactones [67]. Macrocyclic nitrolactones have also been obtained by rearrangement of 2-(3-hydroxypropyl)-2-nitrocycloalkanones using a stoichiometric amount of tetra-*n*-butylammonium fluoride [68].

3.3.21 Macrocyclic lactones (Table 3.17)

Method A (from bromoalkanoates): The potassium ω -bromoalkanoate (0.1 mmol) is suspended in PhMe (1 ml) and TBA-Br is added. The mixture is stirred at 90°C for 3 h. H₂O (10 ml) and PhMe (10 ml) are added and the organic phase is separated, dried (MgSO₄), and evaporated. The residue is extracted with Et₂O (3 × 20 ml) and the extracts are evaporated to yield the lactone.

Method B (from nitrocycloalkanones): The 2-(3-hydroxypropyl)-2-nitrocycloalkanone (0.1 mol) is heated under reflux with TBA-F (31.4 g, 0.12 mol) for 1.5 h. H₂O (50 ml) and

TABLE 3.17
Macrocyclic lactones

$$\text{Br}(\text{CH}_2)_n\text{C O}_2^- \text{K}^+ \longrightarrow \text{Cyclic Lactone}$$

<i>n</i>	TBA-Br	Reaction time	% yield
5	2.5 mmol	3 h	92
7	1.5 mmol	24 h	26
11	1.5 mmol	3 h	95
14	2.5 mmol	3 h	92
15	2.5 mmol	3 h	94

CH_2Cl_2 (50 ml) are added and the organic phase is separated, washed with H_2O (2×25 ml), dried (MgSO_4), and evaporated to yield the lactone.

The standard conversion of alcohols into their xanthate esters through reaction with carbon disulphide and an alkylating agent is improved by the addition of a quaternary ammonium salt [69]. Excellent yields (>90%) are obtained in relatively short reaction times under mild conditions. The formation over relatively short reaction times of *O*-glycosyl xanthates from partly protected glycosides has been described using a stoichiometric amount of the quaternary ammonium salt [70].

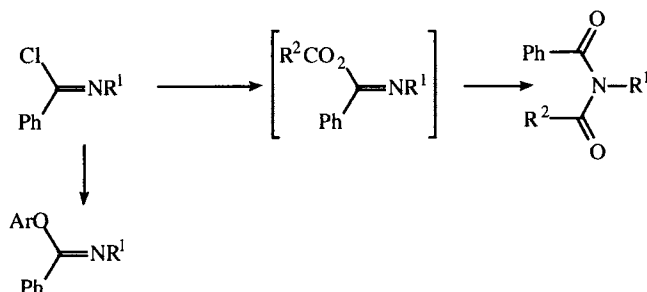
3.3.22 *O*-Alkyl *S*-methyl xanthates

The alcohol (10 mmol) and MeI (1.56 g, 11 mmol) are added to CS_2 (10 ml) and aqueous NaOH (50%, 10 ml) containing TBA- HSO_4 (1 g, 3 mmol) and the mixture is stirred at room temperature. The aqueous phase is separated and extracted with CS_2 (3×10 ml). The combined organic solutions are dried (Na_2SO_4) and evaporated to yield the *O*-alkyl *S*-methyl xanthate, MeSCSOR ($\text{R} = \text{Et}$, reaction time 0.5 h, 87%; $n\text{-C}_8\text{H}_{17}$, 1.5 h, 95%; $n\text{-C}_{16}\text{H}_{33}$, 1 h, 92%; *cyclo*- C_6H_{11} , 1 h, 80%; PhCH_2 , 1 h, 90%; Ph, 1 h, 90%).

3.3.23 *O*-Glycosyl xanthates

The haloalkane (3.3 mmol) in CS_2 (5 ml) is added to a stirred mixture of the glycoside (3 mmol) and TBA- HSO_4 (1.02 g, 3 mmol) in PhH (10 ml) and aqueous NaOH (50%, 10 ml). The reaction is monitored by TLC and, when complete, the mixture is shaken with ice (30 g) and Et_2O (30 ml) and the organic phase is separated. The aqueous phase is extracted with Et_2O (25 ml) and the combined ethereal solutions are washed with H_2O (25 ml), dried (MgSO_4), and evaporated to yield the ester [1,2;3,4-di-*O*-isopropylidene-6-*O*-(alkylthio)-thiocarbonyl- α -D-galactopyranose: alkyl = Me, 92% (45 min), PhCH_2 , 94% (1 h), $\text{CH}_2=\text{CHCH}_2$, 90% (1 h). 1,2;4,6-di-*O*-isopropylidene-3-*O*-(alkylthio)thiocarbonyl- α -D-galactopyranose: alkyl = Me, 94% (45 min), PhCH_2 , 90% (1 h), $\text{CH}_2=\text{CHCH}_2$, 92% (1 h)].

Imidoyl esters (Scheme 3.7) are obtained readily when the appropriate imidoyl chloride is reacted with an alcohol or phenol under basic conditions in the presence of phase-transfer catalysts [71]. The reaction with thiophenol yields the corresponding thioimidoyl ester. Diaroyl amides are produced by the analogous reaction of the imidoyl chloride and carboxylate anions. In this reaction, the initially formed carboxylic ester undergoes a 1,3-migration to produce the amide.



Scheme 3.7

3.3.24 Imidoyl esters

The benzimidoyl chloride (1.6 mmol) in CH_2Cl_2 (10 ml) is added to a stirred mixture of the phenol (2.1 mmol), NaOH (82 mg, 2.1 mmol) and TBA-Br (20 mg, 0.06 mmol) in H_2O (6 ml). The mixture is stirred at room temperature for 1 h and CH_2Cl_2 (20 ml) is then added. The organic phase is separated, washed well with aqueous NaOH (5%) and H_2O , dried (Na_2SO_4), and evaporated to give the imidoyl ester.

3.3.25 Diaroylamides (Table 3.18)

The benzimidoyl chloride (1.3 mmol) in CH_2Cl_2 (10 ml) is added to a stirred mixture of the acid (1.4 mmol), NaOH (55 mg, 1.4 mmol), and TBA-Br (10 mg, 0.03 mmol) in H_2O (10 ml). The mixture is stirred for 3 h at room temperature and then diluted with CH_2Cl_2 (20 ml). The organic phase is separated, dried (Na_2SO_4), and evaporated to yield the amide.

TABLE 3.18
Aryl benzimidates and diaroyl amides

Benzimidoyl chloride $\text{PhC}(\text{NR}^1)\text{Cl}$	% yield of imideate $\text{Ph}(\text{NR}^1)\text{OAr}$		% yield of amide $\text{PhCON}(\text{R}^1)\text{COAr}$	
$\text{R}^1 = \text{Ph}$	Ar = 3- $\text{O}_2\text{NC}_6\text{H}_4$	88	Ar = 3- $\text{O}_2\text{NC}_6\text{H}_4$	89
Ph	4- ClC_6H_4	83	—	—
Ph	4- FC_6H_4	87	—	—
Ph	4- MeOC_6H_4	91	—	—
Ph	—	—	3- BrC_6H_4	86
Ph	—	—	4- $\text{O}_2\text{NC}_6\text{H}_4$	89
Ph	—	—	Ph	91
Me	—	—	Ph	80
Me	2-naphthyl	80	—	—

Trichloroacetimidates, $\text{CCl}_3\text{C}(\text{NH})\text{OR}$, have been prepared under mild conditions by the reactions of alcohols with trichloroacetonitrile under basic conditions promoted by catalytic amounts of tetra-*n*-butylammonium hydrogen sulphate [72]. The procedure is far superior to the standard methods which normally require anhydrous reaction conditions.

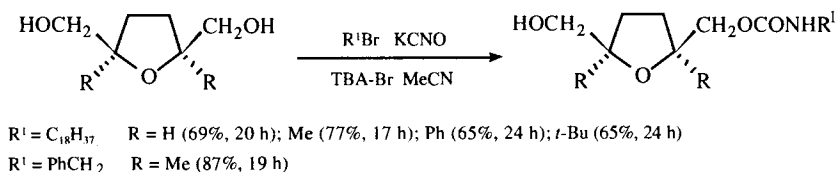
3.3.26 Trichloroacetimidates (Table 3.19)

The alcohol (10 mmol) and TBA- HSO_4 (15 mg, 0.04 mmol) in CH_2Cl_2 (10 ml) are added to aqueous KOH (50%, 10 ml) and the mixture is stirred at *ca.* -15°C for 5 min. CCl_3CN (1.73 g, 12 mmol) is added dropwise and the mixture is stirred for a further 30 min at -15°C and then allowed to come to room temperature over 30 min. The organic phase is separated and the aqueous phase is extracted with CH_2Cl_2 (2×10 ml). The combined organic solutions are dried (Na_2SO_4), concentrated to half volume, and filtered through Celite. Evaporation of the filtrate gave the acetimidate.

TABLE 3.19
 Trichloroacetimidates

Alcohol	% yield of acetimidate	Alcohol	% yield of acetimidate
$\text{CH}_2=\text{CHCH}_2\text{OH}$	80	$n\text{-PrCH(OH)CH}=\text{CH}_2$	93
$\text{MeCH}=\text{CHCH}_2\text{OH}$	93	$\text{PhCH}_2\text{OCH}=\text{CHCH}_2\text{OH}$	97
$n\text{-PrCH}=\text{CHCH}_2\text{OH}$	95	$\text{PhCH}_2\text{OCH}_2\text{CH(OH)CH}=\text{CH}_2$	92
$\text{PhCH}=\text{CHCH}_2\text{OH}$	93	2,3,4,6-Tetra-O-benzyl-	96
PhCH_2OH	97	D-glucopyranose	

Monocarbamylation of diols is generally accomplished only with great difficulty. Reaction of the diol with an alkyl isocyanate is a possibility, but trimerization of the isocyanate frequently occurs [73]. The monocarbamic esters, which have PAF receptor antagonist activity, can be obtained however in acceptable yields via the phase-transfer catalysed *in situ* formation of the alkyl isocyanate from potassium isocyanate and an alkyl halide, and its subsequent reaction with the diol (see Scheme 3.8 for typical examples) [74]. The diols tend to react more rapidly than do simple alcohols and *cis*-diols are more effectively esterified than are *trans*-diols. Additionally, the longer the chain length between the hydroxyl centres, the less effective is the reaction. This has led to the reasonable hypothesis that a cyclic H-bonded intermediate between the two hydroxyl groups and the alkyl isocyanate are critical for the preferential and rapid formation of the carbamate.



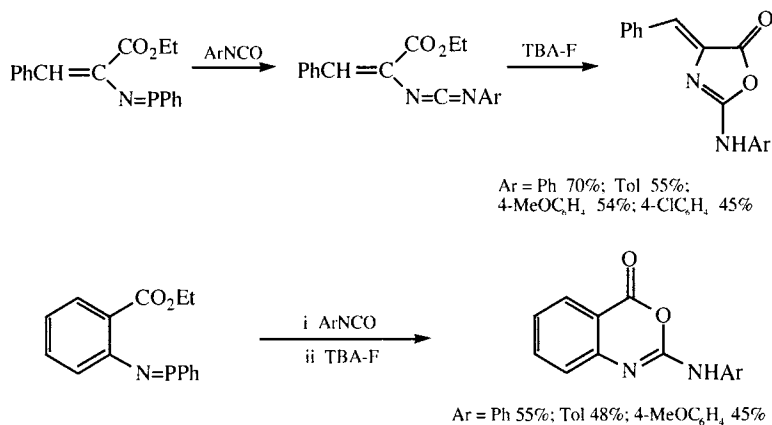
Scheme 3.8

3.3.27 Monocarbamylation of diols

The diol (0.1 mol) in MeCN (50 ml) is added to the haloalkane (0.12 mol), KOCN (12 g, 0.15 mol) and TBA-Br (3.2 g, 10 mmol). The mixture is refluxed at 100 °C under N_2 for 15–24 h and hot CH_2Cl_2 is then added. The mixture is filtered, and evaporated to yield the monocarbamate, which can be purified by flash chromatography.

N-(Ethoxycarbonylmethyl)carbodiimides, obtained from the reaction of iminophosphoranes with aryl isocyanates, undergo cyclization when treated with an excess of tetra-*n*-butylammonium fluoride at room temperature to yield 1,3-oxazolin-5-ones [75] (Scheme 3.9). The ammonium fluoride probably enhances the electrophilic character

of the central carbon atom of the diimide to promote attack by the ester oxygen atom. The iminophosphorane, derived from ethyl anthranilate, is converted into a 3,1-benzoxazin-4-one.



Scheme 3.9

3.3.28 Cyclization of *N*-(ethoxycarbonylmethyl)carbodiimides

The aryl isocyanate (2 mmol) is added to the iminophosphorane (2 mmol) in THF at 0°C and the mixture is stirred under N₂ for 1 h and then allowed to come to room temperature. TBA-F in THF (1M, 8 ml) is added and the solution is stirred at room temperature until the reaction is complete, as shown by TLC analysis (*ca.* 1 h). The solution is evaporated and the residue is washed with a Na₂HPO₄ pH 7 buffer (3 × 25 ml) and extracted with EtOAc (3 × 25 ml). The dried (MgSO₄) extracts are evaporated to yield the cyclic product.

Acyl chlorides are converted in good yield into symmetrical carboxylic acid anhydrides upon treatment with dilute aqueous sodium hydroxide at -10°C in the presence of a tetra-*n*-butylammonium salt [76, 77]. Yields are considerably lower when Aliquat is used. In a similar manner, chloroformates and ethyl oxalyl chloride are converted into carbonic hemi-ester anhydrides.

3.3.29 Carboxylic acid anhydrides (Table 3.20)

Method A: TBA-Cl or TBA-Br (1.8 mmol) in PhMe or CH₂Cl₂ (10 ml) is added to aqueous NaOH (20%, 100 ml) and the mixture is stirred vigorously at -10°C. The acyl chloride (18 mmol) in PhMe or CH₂Cl₂ (50 ml) is then added dropwise over 15–20 min and the mixture stirred for a further period of time until the reaction is complete. AcOH is added to make the mixture neutral and the organic phase is separated, washed well with aqueous Na₂CO₃ and H₂O, dried (MgSO₄), and evaporated to yield the anhydride.

Method B: The acyl chloride (10 mmol), TBA-Br (0.32 g, 1 mmol) and NaHCO₃ (5 g) in MeCN or PhH (10 ml) are stirred for 3–6 h at room temperature and the anhydride (>80%) is isolated as described in 3.3.29.A.

TABLE 3.20

Selected examples of carboxylic acid anhydrides and carbonic hemiester anhydrides

Chloro compound	Reaction conditions	Product	% yield
<i>n</i> -C ₁₃ H ₂₇ COCl	3.3.29/PhMe/3 h	(C ₁₃ H ₂₇ CO) ₂ O	92 ^a
<i>n</i> -C ₁₅ H ₃₁ COCl	3.3.29/PhMe/3 h	(C ₁₅ H ₃₁ CO) ₂ O	90
<i>n</i> -C ₁₆ H ₃₃ COCl	3.3.29/PhMe/3 h	(C ₁₆ H ₃₃ CO) ₂ O	81
<i>t</i> -BuCOCl	3.3.29/CH ₂ Cl ₂ /3 h	(<i>t</i> -BuCO) ₂ O	58
CICO(CH ₂) ₃ COCl	3.3.29/CH ₂ Cl ₂ /30 min	[CO(CH ₂) ₃ CO] ₂ O	76 ^a
CH ₂ =C(Me)COCl	3.3.29/CH ₂ Cl ₂ /3 h	[CH ₂ =C(Me)CO] ₂ O	80 ^a
PhCOCl	3.3.29/PhMe/3 h	(PhCO) ₂ O	95
4-O ₂ NC ₆ H ₄ COCl	3.3.29/CH ₂ Cl ₂ /2 h	(4-O ₂ NC ₆ H ₄ CO) ₂ O	87 ^a
PhCH=CHCOCl	3.3.29/PhMe/3 h	(PhCH=CHCO) ₂ O	80
EtOCOCi	3.3.29/CH ₂ Cl ₂ /1 h	(EtOCO) ₂ O	93
PhCH ₂ OCOCi	3.3.29/Et ₂ O/30 min	(PhCH ₂ OCO) ₂ O	82
EtOCOCOCi	3.3.29/PhMe/15 min	(EtOCOCO) ₂ O	87 ^a

^a Using only 7.5 ml of 20% aqueous NaOH.

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3.4 PHOSPHORIC, SULPHONIC AND OTHER ESTERS

The rate of reaction of phosphorus oxychloride with phenols to produce triaryl phosphates is increased by the addition of quaternary ammonium salts and the reaction temperature can be reduced without loss of overall yield [1,2]. The analogous reaction between phenoxide anions and thiophosphoryl chloride produces aryl phosphorodichloridothoates [3]. As with the acylation of enolizable β -dicarbonyl compounds (3.3.12), phosphorylation leads to the predominant formation of the *E*-*O*-phosphorylated derivatives [4,5].

3.4.1 Triaryl phosphates

POCl_3 (89.3 g, 54 mmol) is added dropwise over *ca.* 20 min to the phenol (0.17 mol) and Aliquat (2.84 g, 7 mmol) in aqueous NaOH (7.5%, 300 ml) and CHCl_3 (250 ml) with vigorous stirring and external cooling. On complete addition of the oxychloride the mixture is stirred for a further 40 min. The organic phase is then separated, washed with aqueous NaOH (2%, 2×100 ml) and H_2O (100 ml), dried (Na_2SO_4), and evaporated to yield the triaryl phosphate (Ar = Ph 89%; 4-MeC₆H₄ 93%; 4-ClC₆H₄ 96%; 4-*t*-BuC₆H₄ 94%; 4-PhC₆H₄ 96%; 1-naphthyl 94%; 2-naphthyl 93%).

3.4.2 Phosphorylation of enolizable β -dicarbonyl compounds (Table 3.21)

The dicarbonyl compound (10 mmol) in CH_2Cl_2 (25 ml) is added with stirring to TBA- HSO_4 (0.68 g, 2 mmol) in aqueous NaOH (2N, 10 ml) at room temperature. Diethyl phosphorochloridate or phosphorochloridothionate (10 mmol) is added dropwise over *ca.* 5 min and the mixture is stirred at room temperature for a further 30 min. The aqueous phase is separated, extracted with CH_2Cl_2 (10 ml). The combined organic solutions are washed with H_2O (2×10 ml), dried (MgSO_4), and evaporated. The residue is taken up in Et_2O and the filtered solution is evaporated to yield the *O*-phosphorylated product.

TABLE 3.21
Phosphorylation of enolizable β -dicarbonyl compounds

	Overall yield	$\begin{array}{c} \text{Me} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ (\text{EtO})_2\text{P}(\text{O})\text{X} \quad \text{COR} \end{array}$	$\begin{array}{c} \text{Me} \quad \text{COR} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ (\text{EtO})_2\text{P}(\text{O})\text{X} \quad \text{H} \end{array}$
<i>Pentan-2,4-dione</i> (R = Me)			
Phosphorylation (X = O)	54%	17%	83%
Thiophosphorylation (X = S)	71%	49%	51%
<i>Ethyl acetoacetate</i> (R = OEt)			
Phosphorylation (X = O)	62%	0%	100%
Thiophosphorylation (X = S)	45%	0%	100%

3.4.3 Aryl phosphorodichloridothioates

PSCl_3 (271 g, 1.6 mol) in CH_2Cl_2 (400 ml) is added at 0°C to a stirred solution of the phenol (0.4 mol) in aqueous NaOH (25%, 350 ml). TBA-Br (3.2 g, 10 mmol) is added and the mixture is stirred at room temperature for *ca.* 8 h. The organic phase is separated, washed with brine (100 ml), dried (MgSO_4), and evaporated to yield the phosphorodichloridothioate ($2\text{-ClC}_6\text{H}_4\text{OPSCl}_2$ 96%; $4\text{-ClC}_6\text{H}_4\text{OPSCl}_2$ 91%).

The catalysed two-phase adaptation of the Atherton–Todd procedure is effective for the phosphorylation of primary alcohols and of phenols [6] to produce trialkyl phosphates and dialkyl aryl phosphates. Trialkyl phosphates have also been obtained in high yield (>75%) from the alkylation of preformed tetra-*n*-butylammonium di-*t*-butylphosphate [7]. Subsequent cleavage of the *t*-butyl groups provide a simple synthesis of monoalkyl phosphates.

3.4.4 Atherton–Todd phosphorylation of alcohols and phenols (Table 3.22)

The dialkyl phosphite (0.25 mmol) in CCl_4 (60 ml) is added dropwise with vigorous stirring at 20°C to aqueous NaOH (50%, 60 ml), TBA-Br (1.6 g, 5 mmol), and the alcohol or phenol (0.2 mmol) in CCl_4 (120 ml). The mixture is stirred for a further 3 h at 20°C and then diluted with CH_2Cl_2 (50 ml). The mixture is filtered and the organic phase is separated from the filtrate, washed with aqueous HCl (2%, 25 ml) and H_2O (2×25 ml), dried (MgSO_4), and evaporated to yield the phosphate.

TABLE 3.22

Selected examples of the Atherton–Todd phosphorylation of alcohols and phenols

% yield of (EtO) ₂ (RO)PO		% yield of (<i>n</i> -BuO) ₂ (RO)PO	
<i>From (EtO)₂POH</i>		<i>From (n-BuO)₂POH</i>	
ROH = <i>n</i> -PrOH	67	ROH = EtOH	71
<i>i</i> -PrOH	37	<i>i</i> -PrOH	35
<i>n</i> -BuOH	71	PhCH ₂ OH	95
PhCH ₂ OH	89	PhOH	94
PhOH	50		

3.4.5 Alkyl di-*t*-butylphosphates

The haloalkane (22 mmol) is added to TBA-(*t*-BuO)₂PO₂ (9 g, 20 mmol), prepared by the reaction of equimolar amounts of (*t*-BuO)₂PO₂K with TBA-HSO₄ in aqueous NaOH (20%), in $\text{MeO}(\text{CH}_2)_2\text{OMe}$ (50 ml) and the mixture is refluxed with stirring for 3 h and then cooled to room temperature. The mixture is filtered and the filtrate is diluted with petroleum ether (30 ml) and washed with aqueous K_2CO_3 (20%, 5 ml), dried (MgSO_4), and evaporated to yield the trialkyl phosphate, (*t*-BuO)₂(RO)PO (e.g. R = *n*-Pr, 88%; *n*-Bu, 78%; $\text{CH}_2=\text{CHCH}_2$, 80%).

Diethyl phosphate esters of the sterically congested phenols of calixarenes have been prepared in acceptable yields (>55%) and used in the preparation of metacyclophanes [8]. The corresponding reaction using diethyl phosphite, with triethylamine in place of the quaternary ammonium catalyst, results in only partial phosphorylation of the hydroxyl groups.

3.4.6 Diethyl aryl phosphates

Aqueous NaOH (50%, 50 ml) is added to the phenolic compound (1.54 mmol), (EtO)₂POCl (9.7 g, 56 mmol) and TBA-Br (0.1 g, 0.3 mmol) in CH₂Cl₂ (100 ml) and the mixture is refluxed for 6 h. The organic phase is separated, washed well with brine, dried (Na₂SO₄), and evaporated to yield the phosphate ester.

O,O-Diaryl benzenephosphonothioates (>80%) and *O,O*-dimethyl *O*-aryl phosphothionates have been synthesized under mild conditions from the reaction of phenols under basic two-phase conditions with benzenephosphonothioic dichloride and dimethyl phosphorochloridothionate, respectively [9, 10]. The reaction with the phosphorochloridothionate requires the catalytic effect of both tetra-*n*-butylammonium bromide and *N*-methylimidazole for the rate to be sufficiently enhanced to make it a viable route to the ester [10].

3.4.7 *O,O*-Diaryl benzenephosphonothioates

Benzenephosphonothioic dichloride (21 g, 0.1 mol) in PhH (50 ml) is added dropwise to the phenol (0.2 mol) and TEBA (2 g, 8.8 mmol) in aqueous NaOH (40%, 20 ml) and the mixture is stirred for 45 min. The organic phase is separated, washed well with H₂O until the washings are neutral, and evaporated to yield the *O,O*-diaryl ester.

3.4.8 *O,O*-Dimethyl *O*-aryl phosphothionates

The sodium phenoxide (0.2 mol) in H₂O (20 ml) is stirred with *O,O*-dimethyl phosphorochloridothionate (32.1 g, 0.2 mol), TBA-Br (0.64 g, 2 mmol) and *N*-methylimidazole (0.17 g, 2 mmol) in CH₂Cl₂ (20 ml) at room temperature. On completion of the reaction the product is isolated as described in 3.4.7.

Polyphosphates and phosphates have also been obtained under phase-transfer catalytic conditions by nucleophilic displacement reactions on haloalkanes, tosyl-oxyalkanes and sulphonium salts by polyphosphate or phosphate anions [e.g. 7, 11–15]. The procedure has been used with success for the phosphorylation of terpenes [11] and nucleosides [12, 13].

3.4.9 Alkyl pyrophosphates from bromoalkanes

(TBA)₃-HP₂O₇ (0.68 g, 0.75 mmol), obtained from Na₂H₂P₂O₇ by exchange on a Dowex 50W-X8 (H⁺ form) column followed by neutralization (to pH 7) with TBA-OH, is added to the bromoalkane (0.75 mmol) in MeCN (6 ml) and the mixture is stirred at room

temperature for 24 h. The mixture is diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (3×15 ml). The extracts are washed well with H_2O , dried (MgSO_4), and evaporated to yield the alkyl pyrophosphate.

3.4.10 Nucleotide 5'-diphosphates from 5'-O-tosyl nucleosides

$(\text{TBA})_3\text{-HP}_2\text{O}_7$ (0.68 g, 0.75 mmol) is added to the nucleoside tosylate (0.5 mmol) in MeCN (0.5 ml) and the solution is stirred at room temperature until the reaction is complete (monitored by NMR spectroscopy). H_2O (1 ml) is added and the solution is filtered through a 0.45- μm Millex filter. The filtrate is purified by linear gradient elution from DEAE Fractogel (eluent: 0.05–0.5 M aqueous NH_4HCO_3) and the desired fractions are dried by lyophilization.

Dialkyl hydrogen phosphites are alkylated in high yield under basic liquid:liquid phase-transfer catalytic conditions via the Michaelis–Becker reaction to yield dialkyl alkylphosphonates without serious side reactions [16, 17].

3.4.11 Michaelis–Becker synthesis of dialkyl alkylphosphonates

$(\text{RO})_2\text{P(O)H}$ (0.11 mol) in CH_2Cl_2 (75 ml) is added dropwise over *ca.* 1 h to the chloroalkane (0.1 mol) and Aliquat or TEBA-Cl (1.8 mmol) in CH_2Cl_2 (20 ml) and aqueous NaOH (50%, 100 ml) and the mixture stirred at *ca.* 5°C until GLC analysis shows the reaction to be complete. CH_2Cl_2 (30 ml) is added and the aqueous phase is separated and extracted with $n\text{-C}_5\text{H}_{12}$ (50 ml). The combined organic solutions are washed with aqueous MeOH (50%, 3×50 ml) and brine (50 ml), dried (Na_2SO_4), and evaporated to yield the dialkyl alkylphosphonate [e.g. $(\text{EtO})_2\text{P(O)CH}_2\text{CO}_2\text{Et}$ (20 min), 55%; $(\text{EtO})_2\text{P(O)CH}_2\text{CO}_2t\text{-Bu}$ (50 min), 70%; $(n\text{-BuO})_2\text{P(O)CH}_2\text{CO}_2t\text{-Bu}$ (1.5 h), 91%].

Sulphonic esters have been obtained from the sulphonyl chlorides in high yields under mild conditions for a range of alcohols and phenols [e.g. 18, 19]. Of particular value is the protection of glycosides possessing a free hydroxyl group and hydroxysteroids, which are tosylated readily under phase-transfer conditions [20–22]. Alkyl sulphinates have been obtained in a similar manner [23]. Alternatively, preformed tetra-*n*-butylammonium sulphonates or their alkali metal salts have also been alkylated with haloalkanes or alkyl fluorosulphonates [24, 25]. In contrast with more classical procedures, tosylation of alcohols, which are susceptible to *E:Z*-isomerism, e.g. *Z*-alk-2-en-1-ols, occurs with retention of their stereochemistry under phase-transfer catalysis [26].

3.4.12 Benzene and 4-toluene sulphonic esters (Table 3.23)

The arene sulphonyl chloride (0.11 mol) in PhH (50 ml) is added dropwise at 20°C to a two-phase system of the alcohol (or phenol) (0.1 mol) and TEBA-Cl (0.91 g, 4 mmol) in PhH (100 ml) and aqueous NaOH (30%, 50 ml). The mixture is stirred at 20°C for 5–8 h, and the organic phase is then separated, washed well with H_2O until the washings are neutral, dried (Na_2SO_4), and fractionally distilled to yield the sulphonic ester.

3.4.13 Methane sulphonic esters (Table 3.23)

MeSO₂Cl (17.1 g, 0.15 mol) in CH₂Cl₂ (50 ml) is added dropwise to a two-phase system of the alcohol (or phenol) (0.1 mol) and TEBA-Cl (0.23 g, 1 mmol) in CH₂Cl₂ (100 ml) and aqueous NaOH (30%, 50 ml), which had been cooled to –5 °C, at such a rate to maintain a reaction temperature below 0 °C. The mixture is stirred for 10 min and then worked up as described in 3.4.12.

TABLE 3.23
Selected sulphonic esters

Alcohol/phenol	% yield of PhSO ₃ R	% yield of 4-MeC ₆ H ₄ SO ₃ R	% yield of MeSO ₃ R
<i>n</i> -BuOH	81	82	74
<i>n</i> -C ₅ H ₁₁ OH	85	—	81
<i>n</i> -C ₆ H ₁₃ OH	82	—	76
<i>n</i> -C ₁₁ H ₂₃ OH	—	88	—
<i>n</i> -C ₁₃ H ₂₇ OH	85	81	—
Me ₂ CHCH ₂ OH	—	—	72
EtCHMeCH ₂ OH	—	—	68
CH ₂ =CHCH ₂ OH	88	—	—
PhOH	85	82	—

3.4.14 Tosylation of glycosides

Aqueous NaOH (5%, 2 ml) is added to the glycoside (0.9 mmol), TBA-HSO₄ (60 mg, 0.18 mmol) and TosCl (0.23 g, 1.3 mmol) in CH₂Cl₂ (25 ml) and the mixture is stirred for *ca.* 30 min at room temperature. When the reaction is complete, as shown by TLC analysis, the organic phase is separated, washed with H₂O (5 ml), dried (Na₂SO₄), and evaporated to yield the glucosyl tosylate.

3.4.15 Alkyl 4-toluenesulphinates

The alkyl halide (20 mmol) is added to anhydrous 4-MeC₆H₄SO₂Na (3.72 g, 21 mmol) and TBA-Br (0.33 g, 1 mmol) in DME (25 ml) and the solution is heated under reflux for *ca.* 30 min. The cooled reaction mixture is poured into ice/H₂O (100 ml) and the precipitated sulphinic ester is collected, washed well with H₂O, and dried (e.g. from *n*-BuBr, 94%; PhCH₂Br, 96%; CH₂=CHCH₂Br, 90%; EtOCOCH₂Cl, 90%; PhCOCH₂Cl, 96%).

When 1,2-diols are subjected to the same reaction conditions required for the formation of sulphonic esters, oxiranes are produced [27]. Presumably, the mono ester is initially formed and, under the basic conditions, intramolecular elimination occurs to produce the oxirane. Partial hydrolysis and ring-closure of α,β-di(tosyloxy) compounds under basic phase-transfer catalytic conditions provides a convenient route to carbohydrate oxiranes [e.g. 28, 29]. Oxiranes have been produced by an analogous method via carbonate esters from partially protected carbohydrates [30].

3.4.16 Oxiranes from 1,2-diols (Table 3.24)

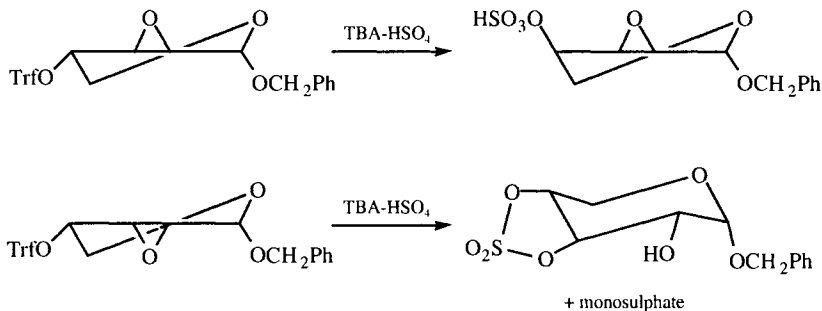
Method A: The diol (0.1 mol) and TEBA-Br (1 g, 3.7 mmol) in CH_2Cl_2 (200 ml) are stirred vigorously with aqueous NaOH (50%, 50 ml) for 15 min. TosCl (19 g, 0.1 mol) in CH_2Cl_2 (100 ml) is added with cooling at 25°C and the mixture is stirred for *ca.* 10 min and then poured into H_2O (200 ml). The organic phase is separated, washed with H_2O (3×50 ml), dried (Na_2SO_4), and evaporated to yield the oxirane.

Method B: Aqueous NaOH (20%, 100 ml) is added to the diol (0.1 mol) and TEBA-Br (1 g, 3.7 mmol) in CH_2Cl_2 (100 ml) and the mixture is stirred and refluxed for *ca.* 10 min. MeSO_2Cl (11.5 g, 0.1 mol) in CH_2Cl_2 (100 ml) is added dropwise and the mixture is stirred for a further period until the reaction is complete, as shown by TLC analysis. The oxirane is isolated as described in 3.4.16.A.

TABLE 3.24
Selected oxiranes from 1,2-diols

R ¹ CH(OH)CH(OH)R ² R ¹ R ²		Reaction conditions	% yield
	-(CH ₂) ₃ -	3.4.16.A/10 min	71
	-(CH ₂) ₄ -	3.4.16.A/10 min	75
	-(CH ₂) ₅ -	3.4.16.A/10 min	82
<i>n</i> -C ₄ H ₉ OCH ₂	H	3.4.16.B/10 min	75
Ph	H	3.4.16.B/20 min	80
Ph	Ph	3.4.16.B/30 min	70
PhO	H	3.4.16.B/10 min	81

Triflate esters of epoxy sugars are cleaved by tetra-*n*-butylammonium hydrogen-sulphate forming the corresponding hydrogensulphate ester (Scheme 3.10). When the epoxy group is *cis* to the triflate ester, concomitant ring opening of the oxirane occurs with predominant formation of the cyclic sulphate [31].

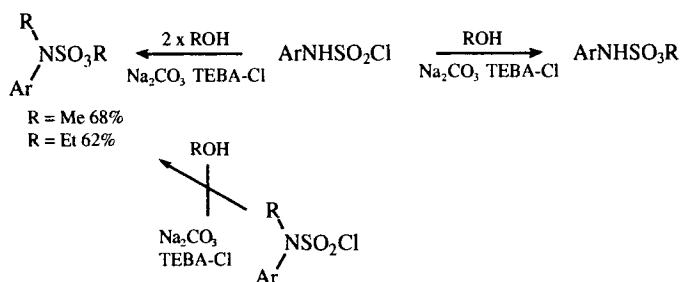


Scheme 3.10

3.4.17 Conversion of triflates into hydrogensulphates

TBA- HSO_4 (0.6 g, 1.77 mmol) is added to the triflate sugar (0.85 mmol) in MeCN (15 ml) at 0°C and the mixture is stirred at room temperature until TLC analysis indicates complete consumption of the triflate ester (ca. 12 h). The solvent is evaporated and the residue recrystallized to yield the hydrogensulphate ester or the cyclic ester.

Relatively few high yielding and convenient procedures are available for the synthesis of sulphamic esters, but the reaction of alcohols with sulphamoyl chlorides under basic conditions in the presence of a phase-transfer catalyst provides a simple route [32]. When the ratio of alcohol to sulphamoyl chloride is increased to 2 : 1, the *N*-alkyl sulphamic ester is produced (Scheme 3.11).



Scheme 3.11

3.4.18 Sulphamic esters (Table 3.25)

The alcohol (5 mmol) or phenol (10 mmol) in PhH or CH_2Cl_2 (5 ml) is cooled to 0°C . Anhydrous Na_2CO_3 (3 g) and TEBA-Cl (0.23 g, 1 mmol) are added, followed by the sulphamoyl chloride (5 mmol) in PhH or CH_2Cl_2 (2.5 ml). The mixture is stirred vigorously for 5 h at 0°C , filtered, and evaporated to yield the sulphamic ester.

TABLE 3.25
Arylsulphamic esters

ArNHSO ₂ Cl	ROH	% yield of ester	ArNHSO ₂ Cl	ROH	% yield of ester
Ar = Ph	R = Me	82	Ar = 4-MeC ₆ H ₄	R = Me	69
	Et	80		Ph	70
	<i>n</i> -C ₆ H ₁₁	28		Et	63
	Ph	88	1-Naphthyl	4-MeC ₆ H ₄	85
	4-MeC ₆ H ₄	75		Me	80
	4-O ₂ NC ₆ H ₄	20		Et	76
	4-PhC ₆ H ₄	10		Ph	70

Alkyl nitrates can be obtained from the catalysed reaction of triflates or tosylates with a quaternary ammonium nitrate [33, 34]. The procedure has been used with success for the preparation of glycosyl nitrates [33].

3.4.19 Nitrate esters

Method A: The alkyl tosylate (10 mmol), NaNO_3 (8.5 g) and TBA-NO_3 (25 g, 82 mmol) in PhH (15 ml) and H_2O (14 ml) are stirred at 110–135 °C in a sealed vessel for 20–96 h. The cooled vessel is opened, when the pressure has returned to normal, and the mixture is poured into H_2O (50 ml) and extracted with EtOAc (2 × 50 ml). The extracts are washed with H_2O (3 × 50 ml), brine (50 ml), dried (MgSO_4) and evaporated. The nitrate ester is purified by flash chromatography from silica [e.g. $\text{MeCH(ONO}_2\text{)CH}_2\text{CO}_2\text{Et}$, 67% (110 °C, 96 h); $\text{Ph(CH}_2\text{)}_2\text{ONO}_2$, 95% (130 °C, 20 h)].

Method B: The triflate (5 mmol) and TBA-NO_3 (3 g, 10 mmol) in PhH or CH_2Cl_2 (50 ml) are refluxed under N_2 for 12–18 h. The cooled reaction mixture is evaporated under reduced pressure and the residue is extracted with CH_2Cl_2 (2 × 25 ml). The extracts are washed sequentially with aqueous HCl (1%), H_2O , aqueous NaHCO_3 (1%) and H_2O , and then dried (Na_2SO_4) and evaporated to yield the nitrate.

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3.5 MISCELLANEOUS REACTIONS

Hydroboration of alkenes in non-ethereal solvent has been reported using diborane generated *in situ* from a quaternary ammonium borohydride and bromoethane (see Section 11.5). Almost quantitative yields of the alcohols are reported [e.g. 1]. As an alternative to the haloalkane, trimethylsilyl chloride has also been used in conjunction with the ammonium borohydride [2]. Reduction of the alkene to the alkane also occurs as a side reaction (<20%) and diphenylethyne is converted into 1,2-diphenylethanol (70%), via the intermediate *trans*-stilbene.

The analogous hydroxylation of alkynes to produce ketones is enhanced by the co-catalytic effect of Aliquat and platinum(IV) chloride-carbon monoxide [3]; it is assumed that $\text{HPtCl}(\text{CO})$ is the active hydration species. C–S and C–Br bonds are cleaved under the reaction conditions.

3.5.1 Hydroxylation of alkenes (Table 3.26)

Me_3SiCl (0.43 g, 4 mmol) in CH_2Cl_2 (2 ml) is added with stirring to the alkene (4 mmol) and TEBA- BH_4 (0.83 g, 4 mmol) in CH_2Cl_2 (6 ml) at 0°C and the mixture is stirred for 0.5–7 h. Aqueous K_2CO_3 (10%, 3 ml) is added and the mixture is stirred for a further 10 min and then extracted with CH_2Cl_2 (2×10 ml). The dried (MgSO_4) extracts are evaporated to yield the alcohol.

TABLE 3.26
Selected examples of the hydroxylation of alkenes

Alkene	Reaction time	Product	% yield
$n\text{-C}_7\text{H}_{15}\text{CH}=\text{CH}_2$	30 min	$n\text{-C}_8\text{H}_{17}\text{CH}_2\text{OH}$	72
cyclo- C_8H_{14}	30 min	cyclo- $\text{C}_8\text{H}_{15}\text{OH}$	74
(+)- α -Pinene	3 h	(-)-Isopinocampheol	74 ^a
Camphene	3 h	<i>endo</i> -Camphanol	80
1-Phenylcyclohexene	4 h	<i>trans</i> -2-Phenylcyclohexanol	63 ^b
$\text{PhCH}=\text{CHPh}$	8 h	$\text{PhCH}_2\text{CH}(\text{OH})\text{Ph}$	78

^a With 10% (+)-neo-isopinocampheol. ^b With 21% *cis*-2-phenylcyclohexanol.

3.5.2 Hydroxylation of alkynes (Table 3.27)

PtCl_4 (50.5 mg, 0.15 mmol) in H_2O (2 ml) is added to Aliquat (0.133 g, 0.33 mmol) in $\text{Cl}(\text{CH}_2)_2\text{Cl}$ (1.5 ml) in an autoclave. The mixture is stirred vigorously under CO (200 psi) at 100°C for *ca.* 20 min and the alkyne (7.5 mmol) is then added and the CO pressure

TABLE 3.27
Selected carbonyl compounds via the hydroxylation of alkynes

Alkyne	Reaction time	Product	% yield
$\text{PhC}\equiv\text{CH}$	3 h	PhCOMe	90
$\text{Ph}(\text{CH}_2)_3\text{C}\equiv\text{CH}$	4 h	$\text{Ph}(\text{CH}_2)_3\text{COMe}$	93
$\text{EtC}\equiv\text{CEt}$	5 h	EtCOPr	84
$\text{PhC}\equiv\text{CPh}$	5 h	PhCH_2COPh	89
$\text{PhC}\equiv\text{CCOPh}$	4.5 h	$\text{PhCOCH}_2\text{COPh}$	97

reduced to 20 psi. The mixture is stirred for a further period at 110°C and the organic phase is then separated, dried (MgSO_4), concentrated, and chromatographed on silica to yield the carbonyl compound.

Thiocarbonyl compounds are converted into the corresponding carbonyl derivatives in good yield (70–99%) by their reaction with concentrated aqueous sodium hydroxide and dichloromethane in the presence of tetra-*n*-butylammonium hydrogen sulphate [4]. The reaction is general for thioesters, thioamides, thioureas and thiones (Table 3.28), and no reaction occurs in the absence of the phase-transfer catalysts. The reaction is also aided by the initial *S*-methylation of the thiocarbonyl group [5].

TABLE 3.28
Conversion of thiocarbonyl compounds into carbonyl derivatives

Thiocarbonyl compound	Reaction time	Product	% yield
PhCSPh	1 h	PhCOPh	90
Thiocamphor	2 h	Camphor	79
MeCS_2Et	7 h	MeCOSEt	99 ^a
PhCSNHPh	3 h	PhCONHPh	51
$\text{Me}_2\text{NCSNMe}_2$	5 h	$\text{Me}_2\text{NCONMe}_2$	75

^a Using 1M aqueous NaOH.

3.5.3 Conversion of thiocarbonyl compounds into carbonyl derivatives

Aqueous NaOH (5M, 20 ml) and TBA- HSO_4 (0.17 g, 0.5 mmol) and CH_2Cl_2 (25 ml) are stirred at room temperature for 30 min. The thiocarbonyl compound (*ca.* 0.2 g) in CH_2Cl_2 (2 ml) is added and the mixture is stirred for a further period of time. The organic phase is separated, washed well with aqueous HCl (2 M) and water, dried (MgSO_4), and evaporated to yield the carbonyl derivative.

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Formation of C–S Bonds and Related Reactions

4.1 SYNTHESIS OF THIOLS, THIOETHERS, THIOACETALS AND S-ALKYL THIOCARBOXYLIC ESTERS

The ‘softer’ electronic character of the thiolate and sulphide anions, compared with the hydroxide ion, results in their greater ability to form ion-pairs with quaternary ammonium cations and, hence, their more efficient transfer into organic solvents.

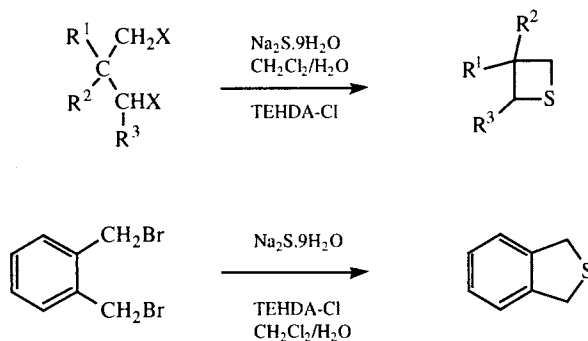
The preparation of thiols by nucleophilic displacement reactions using aqueous potassium or sodium hydrogen sulphide under catalytic conditions is not particularly effective. A limited number of simple alkane thiols have been obtained under mild and neutral conditions in moderate yield (70–80%) from the reaction of bis(*n*-butyltin) sulphide with bromoalkanes in the presence of a *ca.* twofold amount of tetra-*n*-butylammonium fluoride [1], but there has been no exploitation of this procedure.

4.1.1 Alkane thiols

The bromoalkane (2.06 mmol) is added slowly to (*n*-Bu₃Sn)₂S (1.33 g, 2.18 mmol), TBA-F.3H₂O (1.43 g, 4.52 mmol) and H₂O (0.3 ml) in MeCN (12 ml) and the mixture is stirred at 20 °C for *ca.* 20 h. The solvent is evaporated, EtOAc (25 ml) is added to the residue, and the mixture is filtered through silica using EtOAc as an eluent. Flash chromatography of the isolated crude product yields the thiol (e.g. *n*-C₈H₁₇SH, 71%; PhCH₂CH₂SH, 82%).

Although sodium sulphide reacts readily with haloalkanes [2] and activated aryl halides (see Chapter 2) [e.g. 3–5] in the presence of a quaternary ammonium catalyst to form symmetrical thioethers (Table 4.1), a major side reaction results in the formation of disulphides owing to the oxidation of the intermediate thiols under the basic conditions. Consequently, little use has been made of this procedure for the synthesis of thioethers [3, 6], but the corresponding reaction of the α,ω -dihaloalkanes to yield cyclic thioethers has proved to be a valuable procedure for the synthesis of thietanes [7] (Table 4.2). The ring closure with the secondary dihaloalkanes is considerably more difficult to effect than is the reaction of the primary dihaloalkanes. 1,3-Dihydrobenzo[*c*]thiophene (89%) is produced in the reaction of 1,2-bis(bromomethyl)benzene with sodium sulphide (Scheme 4.1) [8]. The direct

conversion of the cyclic thioethers into their *S,S*-dioxides with *m*-perchlorobenzoic acid avoids the difficulties encountered in current literature routes to the oxidized derivative.



Scheme 4.1

TABLE 4.1

Selected examples of the reaction of halopropenes and halopropynes with sodium sulphide

Haloalkane				% yield of thioether
<i>Halopropenes, R¹CH=CR²CHR³X</i>				
R ¹ = H	R ² = H	R ³ = H	X = Cl	94
H	Me	H	Cl	96
Ph	H	H	Br	93 ^a
Me	H	H	Br	24 ^b
H	H	Me	Cl	28 ^c
<i>Halopropynes, RC≡CCH₂X</i>				
R = H	X = Br			73 ^a
Ph	Cl			82 ^d

^a reaction conducted at 20° C. ^b + disulphide (66%). ^c + 31% (MeCH=CHCH₂S)₂ and 25% (MeCH=CHCH₂)₂S. ^d Reaction conducted at 60° C over 15 h.

TABLE 4.2

Synthesis of thietanes from 1,3-dihaloalkanes

XCH ₂ CR ¹ R ² CH(R ³)X				Reaction conditions	% yield of thietane
R ¹	R ²	R ³	X		
H	H	H	Br	4.1.3h/3 h	>70 ^a
OH	H	H	Cl	4.1.3/3 h	81
Me	Me	H	Br	4.1.3/2 h	94
H	H	Me	Br	4.1.3/35 h	57

^a Isolated as *S,S*-dioxide.

4.1.2 Synthesis of symmetrical unsaturated thioethers

$\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (38.4 g, 0.16 mol) in H_2O (80 ml) is added slowly to the haloalkene or alkyne (0.3 mol) and TBA-Cl (3.0 g, 13 mmol) in H_2O (150 ml). The mixture is stirred for 3–4 h at 80°C and then cooled to room temperature. Et_2O (100 ml) is added and the organic phase is separated, dried (Na_2SO_4), and fractionally distilled under reduced pressure to yield the thioether.

4.1.3 Synthesis of thietanes

The 1,3-dihaloalkane (0.4 mol) in CH_2Cl_2 (300 ml) is added to $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (144 g, 0.6 mol), aqueous TEHDA-Cl (50%, 20 ml) in H_2O (350 ml). The mixture is stirred at room temperature until GLC analysis indicates the complete consumption of the haloalkane (ca. 2–3 h for primary dihalopropanes). The organic layer is separated, washed with H_2O (3×25 ml), dried (MgSO_4), and fractionally distilled under reduced pressure to give the thietane.

In contrast with the reactions involving sulphide or hydrogen sulphide anions, aryl alkyl thioethers and unsymmetrical dialkyl thioethers (Table 4.3) are obtained conveniently by the analogous nucleophilic substitution reactions between haloalkanes and aryl or alkylthiols under mildly basic conditions in the presence of a quaternary ammonium salt [9–15] or polymer-supported quaternary ammonium salt [16]. Dimethyl carbonate is a very effective agent in the formation of methyl thioethers (4.1.4.B) [17].

A mild stereoselective synthesis of arylthioglycosides has been accomplished via anomeric inversion during the nucleophilic reaction by aryl thiols on glycosyl halides [18, 19].

4.1.4 Synthesis of unsymmetrical thioethers

Method A: The haloalkane (0.5 mol) is added to the thiol (0.5 mol), NaOH (3.0 g), and Aliquat (0.11 g, 0.25 mmol) in H_2O (10 ml) and the mixture is stirred for 15 min at room temperature. The organic phase is separated, washed with H_2O (2×25 ml), dried (MgSO_4), and evaporated under reduced pressure to yield the thioether.

Method B: $(\text{MeO})_2\text{CO}$ (3.2 g, 35 mmol), the thiol (10 mmol), Aliquat (40 mg, 0.1 mmol) and anhydrous K_2CO_3 (2.1 g) are stirred at ca. 100°C for 8 h. H_2O (20 ml) is added and the mixture is extracted with Et_2O (3×25 ml). The dried (MgSO_4) extracts are evaporated to yield the methyl thioether (68–90%).

Method C: 1-Methyl-3H-imidazol-2-thione (5.7 g, 0.05 mol), the haloalkane (0.05 mol), and TBA-Br (0.97 g, 3 mmol) in aqueous NaOH (40%, 15 ml) are added to PhH (150 ml) and the mixture is stirred for ca. 6 h at 60°C . The organic layer is separated, dried over molecular sieves, and evaporated. The imidazolyl thioether is isolated by distillation under reduced pressure.

Method D: The alkylating agent (1.5 mmol) is added to acrid-9-thione (0.21 g, 1.0 mmol) and TEBA-Cl (23 mg, 0.1 mmol) in a two-phase system of CH_2Cl_2 (10 ml) and aqueous NaOH (25%, 10 ml) at 0 – 5°C and the mixture is stirred until no thiol can be detected by TLC analysis (ca. 15 min). The mixture is poured into H_2O (10 ml) and the organic layer

is separated, washed sequentially with aqueous HCl (2M, 10 ml) and H₂O (10 ml), dried (MgSO₄), and evaporated under reduced pressure to yield the 9-acridyl thioether.

Method E: TBA-Br (0.1 g, 0.3 mmol) in aqueous NaOH (30%, 50 ml) is added to the *S*-alkyl isothiuronium chloride (or bromide) (30 mmol) and the alkylating agent (30 mmol) in PhH (50 ml) and the mixture is stirred for 30–40 min at room temperature. The aqueous phase is separated and extracted with PhH (3 × 40 ml) and the combined organic solutions are washed with H₂O (2 × 10 ml), dried (Na₂SO₄), and evaporated to yield the thioether.

TABLE 4.3
Selected examples of the synthesis of unsymmetrical thioethers

Thiol	Alkylating agent	Method	% yield of thioether
<i>n</i> -BuSH	EtBr	4.1.5.A	90
	<i>n</i> -C ₈ H ₁₇ Br	4.1.5.E	89
	ClCH ₂ CO ₂ Et	4.1.5.E	86
	PhCH=CHCH ₂ Cl	4.1.5.E	89
<i>iso</i> -PrCH ₂ SH	<i>n</i> -C ₈ H ₁₇ Br	4.1.5.A	89
PhCH ₂ SH	MeI	4.1.5.E	91
	<i>n</i> -C ₄ H ₉ Br	4.1.5.E	98
	<i>n</i> -C ₈ H ₁₇ Br	4.1.5.E	97
	ClCH ₂ CO ₂ Et	4.1.5.E	94
	Cl(CH ₂)NH ₂	4.1.5.E	90
	PhCOCH ₂ Br	4.1.5.E	96
	CH ₂ =CHCH ₂ Cl	4.1.5.E	96
	ClCH ₂ CO ₂ Et	4.1.5.E	84
	MeI	4.1.5.A	93
	EtI	4.1.5.A	93
CH ₂ =CHCH ₂ SH PhSH	Et ₃ SO ₄	4.1.5.A	87
	<i>iso</i> -PrBr	4.1.5.A	88
	<i>iso</i> -PrCH ₂ Br	4.1.5.A	85
	<i>n</i> -C ₈ H ₁₇ Br	4.1.5.A	94
	EtBr	4.1.5.C ^{a,b}	90 ^d
	<i>n</i> -PrBr	4.1.5.C	68 ^d
	<i>iso</i> -PrBr	4.1.5.C ^b	64 ^d
	<i>n</i> -BuCl	4.1.5.C	80 ^d
	<i>n</i> -BuBr	4.1.5.C	82 ^d
	cyclo-C ₅ H ₁₁ Br	4.1.5.C ^b	55 ^d
	<i>n</i> -C ₁₂ H ₂₅ Br	4.1.5.C	15 ^d
	CH ₂ =CHCH ₂ Br	4.1.5.C ^b	65 ^d
	PhCH ₂ Cl	4.1.5.C ^b	57 ^d
	PhCH ₂ Br	4.1.5.C ^c	54 ^d
10 <i>H</i> -Acrid-9-thione	Br(CH ₂) ₂ Br	4.1.5.C ^b	73 ^d
	Me ₂ SO ₄	4.1.5.D	95 ^{e,f}
	Et ₃ SO ₄	4.1.5.D	90 ^{e,f}
	PhCH ₂ Cl	4.1.5.D	98 ^e
	CH ₂ =CHCH ₂ Br	4.1.5.D	90 ^{e,f}

^a Reaction conducted at 30°C. ^b Requires reaction time of 20–24 h. ^c Requires reaction time of 48 h. ^d 2-imidazolyl thioethers. ^e 9-acridyl thioethers. ^f Reaction with corresponding 1,3,6,8-tetrahalo derivatives gives similar yields, but requires reaction times of ca. 2 h at 25°C.

4.1.5 Glycosyl thioethers

The aryl thiol (1 mmol) in aqueous Na_2CO_3 (1 M, 1.3 ml) is added to the glycosyl chloride (0.25 mmol) and TBA- HSO_4 (85 mg, 0.25 mmol) in EtOAc, CH_2Cl_2 , or PhMe (1.3 ml) and the mixture is stirred vigorously until the reaction is complete (*ca.* 0.5–1 h). CH_2Cl_2 (15 ml) is added and the organic phase is separated, washed with aqueous Na_2CO_3 (sat. soln., 3×20 ml), H_2O (2×20 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated to yield the thioether.

In an extension of the procedure, thiols react with *gem*-dihaloalkanes (Table 4.4) to produce thioacetals [10, 20–23] and the reaction can be employed in the Corey–Seebach synthesis of aldehydes and ketones (see ref. 24 and references cited therein). *gem*-Dichlorocyclopropanes having an electron-withdrawing group at the 2-position react with thiols to produce the thioacetals [25]. In the corresponding reaction of the thiols with bromochloromethane exclusive nucleophilic substitution of the bromo group by the thiolate anion occurs to yield the chloromethyl thioethers [13, 14] (Table 4.5).

TABLE 4.4
Synthesis of thioacetals from *gem*-dichloroalkanes^a

Thiol	Dichloroalkane (RCH_2Cl_2)	% yield of thioacetal ^a
EtSH	R = CO_2Et	98
EtSH	CO_2Me	92
$\text{HS}(\text{CH}_2)_2\text{SH}$	CO_2Et	82
$\text{HS}(\text{CH}_2)_3\text{SH}$	CO_2Et	63
PhSH	CO_2Et	89
4-Me-1,2-(HS) $_2$ C $_6$ H $_3$	CO_2Et	83
<i>n</i> -BuSH	H	90
<i>i</i> -PrCH $_2$ SH	H	95
PhSH	H	94 ^b
1,2-(HS) $_2$ C $_6$ H $_4$	H	78
4-Me-1,2-(HS) $_2$ C $_6$ H $_3$	H	61

^a Using 4.1.6.A. ^b 81% using 4.1.6.B.

TABLE 4.5
Selected examples of the synthesis of chloromethyl thioethers

Thiol	% yield of thioether
PhSH	57
4- <i>t</i> -BuC $_6$ H $_4$ SH	60
2,4,6-Br $_3$ C $_6$ H $_2$ SH	91
2,3,5,6-F $_4$ C $_6$ HSH	82
2,3,4,5,6-Cl $_5$ C $_6$ SH	46
3,5-Cl $_2$ -4-(4-ClC $_6$ H $_4$)C $_6$ H $_2$ SH	95
Quinolin-2-thione	43
Benzothiazol-2-thione	58
Pyrimid-2-thione	58
2,5-Dimercapto-3,4-thiadiazole ^a	78
4-Cyano-3,5-dimercaptoisothiazole ^a	60

^a Direct reaction between CH_2ClBr and the potassium salt in the absence of KOH.

4.1.6 Synthesis of thioacetals

Method A: The *gem*-dihaloalkane (0.02 mol) and the thiol (0.04 mol) in PhMe (25 ml) containing Aliquat (20 mg, 0.05 mmol) are added to dry K_2CO_3 (10 g). The mixture is stirred for 8 h at room temperature and then filtered. The filtrate is fractionally distilled under reduced pressure to yield the thioacetal.

Method B: Finely ground KOH (1.94 g, 30 mmol) and PhSH (2.6 ml, 25 mmol) are shaken together for 10 min. CH_2Cl_2 (1.0 g, 10 mmol) is added and the mixture is heated in a stoppered vessel at 60°C for 24 h. The mixture is cooled, Et_2O (150 ml) is added, and the mixture is filtered through Florisil (2.0 g). Fractional distillation of the filtrate gives the thioacetal.

4.1.7 Synthesis of chloromethyl thioethers

The thiol (25 mmol) is added with stirring to KOH (1.94 g, 30 mmol) in CH_2BrCl (150 ml). Upon addition of TEBA-Br (0.3 g, 1.1 mmol), the reaction becomes exothermic and the mixture is stirred at room temperature for 2 h and then filtered. Excess CH_2BrCl is removed under reduced pressure and the residue is extracted with Et_2O (75 ml). The dried ($MgSO_4$) ethereal solution is diluted with $n-C_6H_{14}$ (50 ml) and evaporated to yield the chloromethyl thioether.

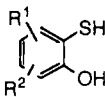
Ketene dithioacetals are obtained in very good yield (>95%) from the disodium salt of 2-cyanoethene-1,1-dithiolate with a range of alkylating agents in the presence of tetra-*n*-butylammonium bromide [26].

4.1.8 3,3-Bis(alkylthio)propenenitriles

The alkylating agent (50 mmol) is added to the disodium salt of 2-cyanoethene-1,1-dithiolate (25 mmol) in H_2O (15 ml) and the mixture is stirred at room temperature until the mixture becomes solid (the reaction may initially become exothermic). The product is collected by filtration, washed well with H_2O , and dissolved in CH_2Cl_2 / $n-C_6H_{14}$ (1 : 1, 10 ml). The solution is filtered through silica and evaporated to yield the thioacetal, $(RS)_2C=CHCN$ (e.g. R = Me, 96%; $PhCH_2$, 97%; $(CH_2)_2$, 96%).

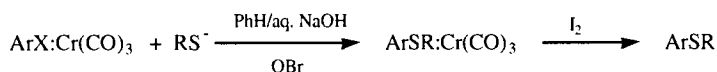
TABLE 4.6

Selected examples of 1,3-benzoxathioles from 2-hydroxythiophenols

		% yield of 1,3-benzoxathiole
R ¹ = H	R ² = H	73
3-Me	H	76
4-Me	H	78
5-Me	H	75
4-Me	6-Me	81
5-Cl	H	70

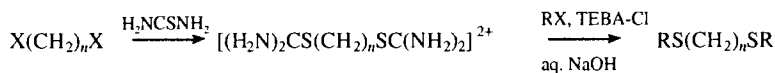
2-Hydroxythiophenols react with dibromomethane to produce 1,3-benzoxathioles [27] (Table 4.6). 1,3-Benzoxathioles have also been obtained by the one-pot base-catalysed ring opening of 1,3-benzoxathiol-2-ones and subsequent reaction with dibromomethane in the presence of Aliquat [28].

Activated aryl halides react with thiols [e.g. 4] to produce aryl thioethers and thioethers, derived from non-activated aryl halides, can be synthesized via the $\text{Cr}(\text{CO})_3$ complexes of the haloarenes [29] (Scheme 4.2, see also Chapter 2).



Scheme 4.2

The conversion of *S*-alkyl isothiuronium salts into thioethers is aided by the addition of a phase-transfer catalyst (4.1.4.E) [30]. Similarly, α,ω -dihaloalkanes are converted in a one-pot reaction into bis-sulphides (> 90%) via the isothiuronium salts (Scheme 4.3) [31].



Scheme 4.3

4.1.9 Synthesis of symmetrical bis-sulphides

The dihaloalkane (10 mmol) is added to thiourea (20 mmol) in EtOH (25 ml) over 10 min and then stirred under reflux for *ca.* 3 h. The EtOH is removed under reduced pressure and aqueous NaOH (20%, 30 ml), TEBA-Cl (0.11 g, 0.5 mmol), and the haloalkane (20 mmol) is added. The mixture is heated at 60°C for *ca.* 1.5 h and then cooled, filtered, and acidified to pH 2.0 with aqueous HCl (6M) to yield the bis-sulphide.

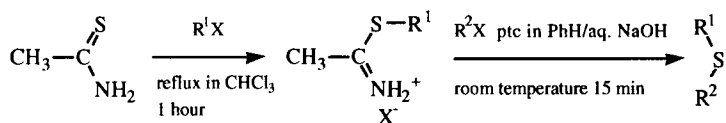
4.1.10 Synthesis of 1,3-benzoxathioles

Method A from thiophenols: The thiophenol (0.2 mol) and NaOH (20 g, 0.5 mol) in H_2O (100 ml) are added dropwise over a period of *ca.* 4.5 h to Adogen (0.9 g, 2 mmol) in a refluxing two-phase system of H_2O (40 ml) and CH_2Br_2 (52 g, 0.3 mol). The mixture is stirred under reflux for 5 h and then poured into H_2O (50 ml) and extracted with Et_2O (3×25 ml). The dried (Na_2SO_4) extracts are evaporated and the product is distilled under reduced pressure.

Method B from 1,3-benzoxathiol-2-ones: NaHCO_3 (12.6 g, 0.15 mol) and Aliquat (1.5 g, 3.7 mmol) in H_2O (35 ml) are added to the 1,3-benzoxathiol-2-one (0.05 mol) in CH_2Br_2 (10 ml) and the mixture is refluxed for 3 h. Excess CH_2Br_2 (*ca.* 8 ml) is then allowed to distil and the reaction temperature is raised to *ca.* 100°C and maintained at this temperature until TLC analysis shows complete disappearance of the benzoxathiolone. The reaction mixture is extracted with Et_2O (2×25 ml) and the ethereal extracts

are washed with H₂O, dried (MgSO₄), and evaporated. The benzoxathiole is purified by chromatography from silica.

A superior and relatively versatile procedure for the synthesis of unsymmetrical dialkyl thioethers, which avoids the unattractive direct use of thiols, utilizes the stable 1-alkylthioethaniminium halides, which are readily obtained from thioacetamide [32] (Scheme 4.4). The reaction has also been used for the synthesis of alkyl aryl thioethers from activated aryl halides [33], but it cannot be used for the synthesis of cyclic thioethers, as polymeric sulphides are formed from α,ω -dihaloalkanes. A similar sequence to that which leads to the thioethers has been used for the synthesis of *S*-alkyl thioesters [34] (see 4.1.26).



Scheme 4.4

4.1.11 Synthesis of unsymmetrical dialkyl thioethers from 1-alkylthioethaniminium halides (Table 4.7)

The haloalkane (10 mmol), TBA-Br (79 mg, 0.3 mmol) in PhH (50 ml) and freshly prepared 1-alkylthioethaniminium halide (10 mmol), obtained by refluxing thioacetamide

TABLE 4.7

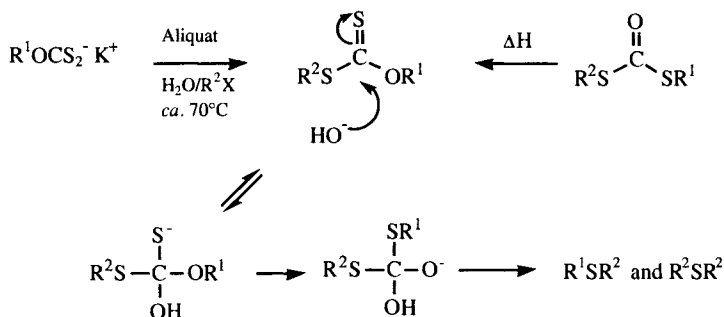
Selected examples of unsymmetrical thioethers from thioacetamide

1-Alkylthioethaniminium halide [R ¹ SC(Me)=NH ₂] ⁺ X ⁻		Haloalkane	% yield of thioether
R ¹ = <i>n</i> -Bu	X = Br	<i>iso</i> -BuBr	88
		4-MeC ₆ H ₄ CH ₂ Br	82
<i>n</i> -C ₈ H ₁₇	Br	EtBr	90
		<i>n</i> -BuBr	91
		PhCH ₂ Br	91
		4-MeC ₆ H ₄ CH ₂ Br	95
CH ₂ =CH(CH ₂) ₂	Br	ClCH ₂ CO ₂ Et ^a	77
PhCH ₂	Br	EtBr	80
		<i>n</i> -BuBr	97
		<i>n</i> -C ₈ H ₁₇ Br	92
		CH ₂ =CHCH ₂ Br ^a	80
		ClCH ₂ CO ₂ Et ^a	86
		4-MeC ₆ H ₄ CH ₂ Cl	96
		4-ClC ₆ H ₄ CH ₂ Cl	95
		4-NO ₂ C ₆ H ₄ CH ₂ Cl	100
		4-MeC ₆ H ₄ CH ₂ Cl	92
		4-ClC ₆ H ₄ CH ₂ Cl	100
4-MeC ₆ H ₄ CH ₂	Cl	4-NO ₂ C ₆ H ₄ CH ₂ Cl	100

^a 90 h reaction time.

(3.75 g, 50 mmol) and the haloalkane (50 mmol) in CHCl_3 (50 ml) for 1 h, in aqueous NaOH (30%, 50 ml) are stirred at room temperature for 15 min. The organic layer is separated, washed with H_2O (3×50 ml), dried (Na_2SO_4), and fractionally distilled to give the thioether.

An alternative procedure for the synthesis of unsymmetrical thioethers, which is equally versatile and also avoids the direct use of thiols, utilizes *O,S*-dialkyl [35] or *S,S*-dialkyl dithiocarbonates [36] (Scheme 4.5).



Scheme 4.5

Trifluoromethyl thioethers are produced in a fluoride-catalysed one-pot reaction of alkyl or aryl thiocyanates with trifluoromethyl silanes [37]. The reaction is initiated by fluoride ion displacement of the trifluoromethyl anion from the silane; the thioether is formed from the thiocyanate by displacement by the trifluoromethyl anion of the cyanide ion, which then perpetuates the reaction. Trifluoromethyl selenoethers are obtained by an analogous route. In a similar manner, disulphides can be converted into trifluoromethyl thio- or selenoethers [38].

4.1.12 Trifluoromethyl thioethers

TBA-F (1M in THF, 1 ml, 1 mmol) is added dropwise to the thiocyanate (10 mmol) and CF_3SiMe_3 (1.42 g, 10 mmol) in THF (10 ml) at 0°C . The mixture is stirred at 0°C for 5 min and then at room temperature for 2.5 h. The reaction mixture is worked-up as described in 4.1.11 to yield the trifluoromethyl thioether (e.g. $\text{PhCH}_2\text{SCF}_3$, 87%; $\text{C}_8\text{H}_{17}\text{SCF}_3$, 76%; PhSCF_3 , 70%; $\text{cyclo-C}_6\text{H}_{11}\text{SCF}_3$, 33%).

The *O,S*-dialkyl dithiocarbonates (Table 4.8) are readily prepared under phase-transfer catalytic conditions by the reaction of an alkylating agent with potassium *O*-alkyl dithiocarbonate [35, 39], which can be obtained from carbon disulphide and the appropriate potassium alkoxide [cf. 40]. Monosaccharides are converted into *S*-glycosyl dithiocarbonates via the *in situ* formation of the tosylate, followed by reaction with potassium *O*-alkyl dithiocarbonate (Scheme 4.6) [41]. In a similar manner, *S*-glycosyl *N,N*-diethyldithiocarbamates are obtained from the monosaccharide and *N,N*-diethyldithiocarbamate (see 4.3.2) [42].

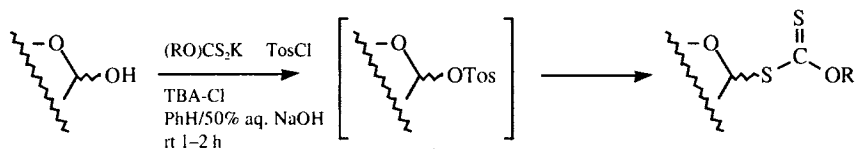
TABLE 4.8
Synthesis of *O,S*-dialkyl dithiocarbonates

Alkylating agent	Reaction conditions	% yield
<i>From potassium O-methyl dithiocarbonate</i>		
<i>n</i> -C ₈ H ₁₇ Br	4.1.14/5 min/25 °C	60 ^a
<i>From potassium O-ethyl dithiocarbonate</i>		
<i>n</i> -PrI	4.1.14/5 min/70 °C	88
<i>n</i> -BuI	4.1.14/5 min/70 °C	91
<i>n</i> -BuBr	4.1.14/5 min/70 °C	85
<i>n</i> -BuOMes	4.1.14/5 min/70 °C	82
<i>n</i> -C ₈ H ₁₇ I	4.1.14/10 min/25 °C	93 ^b
<i>n</i> -C ₈ H ₁₇ Br	4.1.14/20 min/25 °C	90 ^c
<i>n</i> -C ₈ H ₁₇ Cl	4.1.14/48 h/25 °C	58 ^d
<i>n</i> -C ₈ H ₁₇ O Mes	4.1.14/60 min/25 °C	90 ^e
<i>n</i> -C ₆ H ₁₃ CH(Me)I	4.1.14/10 min/70 °C	81 ^f
<i>n</i> -C ₆ H ₁₃ CH(Me)Br	4.1.14/24 h/25 °C	68 ^e
<i>n</i> -C ₆ H ₁₃ CH(Me)OMes	4.1.14/16 h/25 °C	88 ^g
<i>n</i> -C ₁₆ H ₃₃ Br	4.1.14/5 min/70 °C	100
CH ₂ =CHCH ₂ Cl	4.1.14/10 min/25 °C	91
PhCH ₂ Cl	4.1.14/10 min/25 °C	90
<i>From potassium O-n-octyl dithiocarbonate</i>		
EtI	4.1.14/10 min/25 °C	81
<i>n</i> -C ₁₆ H ₃₃ Br	4.1.14/5 min/70 °C	92
<i>From potassium O-iso-propyl dithiocarbonate</i>		
<i>n</i> -C ₈ H ₁₇ I	4.1.14/6 min/25 °C	86
<i>n</i> -C ₈ H ₁₇ Br	4.1.14/5 min/70 °C	94 ⁱ
<i>n</i> -C ₈ H ₁₇ Cl	4.1.14/1 h/70 °C	83 ^j
<i>n</i> -C ₈ H ₁₇ OMes	4.1.14/5 min/70 °C	86
<i>n</i> -C ₆ H ₁₃ CH(Me)Br	4.1.14/25 min/70 °C	86 ^k
<i>n</i> -C ₆ H ₁₃ CH(Me)OMes	4.1.14/10 min/70 °C	86 ^l
<i>n</i> -C ₁₆ H ₃₃ Br	4.1.14/5 min/70 °C	100
<i>From potassium O-t-butyl dithiocarbonate</i>		
<i>n</i> -C ₈ H ₁₇ Br	4.1.14/5 min/25 °C	93

^a 70% (25 min at 25 °C). ^b 91% (5 min at 70 °C). ^c 85% (5 min at 70 °C). ^d 47% (45 min at 70 °C).

^e 86% (5 min at 70 °C). ^f 80% (2 h at 25 °C). ^g 60% (25 min at 70 °C). ^h 72% (12 min at 70 °C).

ⁱ 88% (25 min at 25 °C). ^j 87% (48 h at 25 °C). ^k 88% (12 h at 25 °C). ^l 87% (8 h at 25 °C).



4.1.13 *O*-Alkyl *S*-glycosyl dithiocarbonates

The monosaccharide (1 mmol), TBA-Cl (70 mg, 0.25 mmol) and TosCl (0.29 g, 1.5 mmol) in PhH (15 ml) are stirred with potassium *O*-alkyl dithiocarbonate (1 mmol) and aqueous NaOH (50%, 10 ml) at room temperature for *ca.* 2 h. The organic phase is

separated, washed well with H_2O , dried (Na_2SO_4), and evaporated to yield the *S*-glycosyl derivative.

Symmetrical *S,S*-dialkyl dithiocarbonates have been obtained by thermal rearrangement of the corresponding *O,S*-dialkyl esters in the presence of Aliquat [43]. This procedure is not suitable for the preparation of unsymmetrical *S,S*-dialkyl dithiocarbonates, as it has been reported that disproportionation of the products can lead to a mixture of the symmetrical and unsymmetrical esters. Alternatively, they can be prepared by a base-catalysed disproportionation of *S*-alkyl-*O*-methyl dithiocarbonates [44] (Table 4.9). These methods for the synthesis of the *S,S*-dialkyl esters are more convenient than the traditional procedures from the thiol and phosgene.

TABLE 4.9
Synthesis of symmetrical *S,S*-dialkyl dithiocarbonates from
potassium *O*-methyl dithiocarbonate

<i>S</i> -alkyl groups	Method	% yield
<i>n</i> -Bu	4.1.15	56
<i>n</i> -C ₈ H ₁₇	4.1.15	70
<i>n</i> -C ₁₂ H ₂₅	4.1.15	88
<i>n</i> -C ₁₆ H ₃₃	4.1.15	85
PhCH ₂	4.1.15	70
4-MeC ₆ H ₄ CH ₂	4.1.15	78
4-ClC ₆ H ₄ CH ₂	4.1.15	50

TABLE 4.10
Synthesis of symmetrical dialkyl trithiocarbonates

Haloalkane	Reaction conditions	% yield
<i>n</i> -BuBr	4.1.17 ^a /1 h	90
<i>n</i> -C ₈ H ₁₇ Cl	4.1.17 ^{a,b} /3 h	92
	4.1.17 ^{b,c} /5 h	96
<i>n</i> -C ₈ H ₁₇ Br	4.1.17 ^a /1.5 h	100
	4.1.17 ^{b,c} /3 h	97
<i>n</i> -C ₈ H ₁₇ I	4.1.17 ^{a,b} /3 h	90
<i>n</i> -C ₁₂ H ₂₅ Br	4.1.17 ^a /1.5 h	97
<i>n</i> -C ₁₈ H ₃₃ Br	4.1.17 ^a /1.5 h	100
PhCH ₂ Cl	4.1.17 ^a /1 h	91
4-ClC ₆ H ₄ CH ₂ Cl	4.1.17 ^a /15 min	98
4- <i>t</i> -BuC ₆ H ₄ CH ₂ Br	4.1.17 ^a /30 min	100
<i>iso</i> -PrBr	4.1.17 ^{a,b} /2 h	90
<i>n</i> -PrCH(Me)Br	4.1.17 ^{a,b} /6 h	90
	4.1.17 ^{b,c} /6 h	90
cyclo-C ₅ H ₁₁ Br	4.1.17 ^a /3 h	95
CH ₂ =CHCH ₂ Cl	4.1.17 ^{a,d} /2 h	90
CH ₃ =CHCH ₂ Br	4.1.17 ^a /15 min	90
Cl(CH ₂) ₂ Cl	4.1.17 ^a /1.5 h	93

^a Using Aliquat. ^b 2.5 mol of catalyst used. ^c Using TBA-Br. ^d Room temperature reaction.

Symmetrical dialkyl trithiocarbonates can be obtained in almost quantitative yield from a one-pot two-phase reaction of aqueous sodium sulphide, carbon disulphide, and a haloalkane in the presence of Aliquat [40] (Table 4.10). The corresponding reaction of α,ω -dihaloalkanes in the presence of tetra-*n*-butylammonium hydrogen sulphate yields cyclic trithiocarbonates [45], whereas the analogous reaction of a thiol and carbon disulphide, followed by an alkylating agent, produces the unsymmetrical ester [40, 46, 47] (see Tables 4.11 and 4.12). Poorer yields are obtained in the one-pot reaction from thiophenols, presumably as a result of their weaker nucleophilic character, compared with alkane thiols. In such circumstances, the formation of aryl alkyl thioethers is a significant side reaction (10–50%) [46]. α,ω -Bis-thiols react in an analogous manner with carbon disulphide and an alkylating agent to produce α,ω -bis-trithiocarbonates [48].

4.1.14 Synthesis of *O,S*-dialkyl dithiocarbonates

The alkylating agent (50 mmol) is added to a stirred solution of potassium *O*-alkyl dithiocarbonate (50 mmol) and Aliquat (1.68 g, 4 mmol) in H₂O (50 ml). The mixture is stirred until the aqueous phase is completely colourless (Table 4.8) and petroleum ether (b.p. 40–60°C, 150 ml) is then added. The organic layer is separated, dried (MgSO₄), filtered through silica, and evaporated under reduced pressure to yield the *O,S*-dialkyl ester.

4.1.15 Synthesis of symmetrical *S,S*-dialkyl dithiocarbonates from potassium *O*-methyl dithiocarbonate

The *S*-alkyl-*O*-methyl dithiocarbonate, prepared by procedure 4.1.14 from MeOCS₂K (48.26 g, 0.33 mol), is extracted from the reaction mixture with Et₂O (3 × 25 ml). The ethereal extracts are washed with H₂O (3 × 100 ml) and evaporated under reduced pressure at 40°C. Aqueous Na₂CO₃ (2%, 300 ml) is added and the aqueous mixture is stirred at 50°C for *ca.* 3 h. The mixture is then extracted with Et₂O (3 × 50 ml) and the dried (Na₂SO₄) extracts are evaporated under reduced pressure at 70°C. The temperature of the residue is maintained at 70°C for 30 min and the *S,S*-dialkyl ester, which is contaminated with the *O,S*-dialkyl ester, the dialkyl sulphide and the disulphide, is isolated by chromatography from silica.

4.1.16 Thermal rearrangement of *O,S*-dialkyl dithiocarbonates to give the *S,S*-dialkyl esters

The *O,S*-dialkyl dithiocarbonate (0.1 mol), prepared by procedure 4.1.14, and Aliquat (0.81 g, 2 mmol) are heated at 100°C for *ca.* 90 min. The organic phase is filtered through silica using petroleum ether (b.p. 40–60°C) as the eluent to produce the *S,S*-dialkyl ester (Me, 90%; Et, 85%; *n*-Bu, 76%; *n*-C₈H₁₇, 79%; PhCH₂, 70%).

4.1.17 Synthesis of symmetrical dialkyl trithiocarbonates

CS₂ (7.6 g, 0.1 mol) is stirred with Na₂S.9H₂O (24 g, 0.1 mol), and Aliquat (0.2 g, 0.5 mmol) in H₂O (30 ml) at room temperature for 90 min. The haloalkane (0.2 mol) is added and the mixture is stirred at 70°C (Table 4.10). The mixture is then cooled to room temperature and petroleum ether (b.p. 40–60°C) is added. The organic phase is sepa-

rated, dried (MgSO_4), filtered through silica, and evaporated under reduced pressure to yield the dialkyl trithiocarbonate.

4.1.18 Synthesis of dialkyl and alkyl aryl trithiocarbonates

Method A: CS_2 (7.6 g, 0.1 mol) and Aliquat (0.2 g, 0.5 mmol) are added to the alkanethiol (0.1 mol) in aqueous KOH (20%, 30 ml) and the mixture is stirred for 15 min at room temperature. The haloalkane (0.1 mol) is added and the mixture is stirred at 70°C (Table 4.11). The dialkyl trithiocarbonate is isolated by the procedure described in 4.1.17.

Method B: CS_2 (1.5 g, 20 mmol) and Aliquat (12 mg, 0.3 mmol) are added to the arenethiol (10 mmol) in aqueous NaOH (10%, 5 ml) and the mixture is stirred at room temperature for 2 h. The haloalkane (10 mmol) in PhH (10 ml) is added and the mixture is stirred for a further 3 h at room temperature. The organic phase is separated, dried (Na_2SO_4), and evaporated under reduced pressure. The crude product is distilled or chromatographed from silica to give the alkyl aryl trithiocarbonate (Table 4.12).

TABLE 4.11
Unsymmetrical and symmetrical dialkyl trithiocarbonates from thiols

Thiol	Haloalkane	Reaction time	% yield
<i>iso</i> -PrSH	<i>n</i> -C ₈ H ₁₇ Br	15 min	100 ^a
<i>n</i> -BuSH	<i>n</i> -BuBr	15 min	95
	<i>n</i> -C ₈ H ₁₇ Cl	7 h	80 ^b
	<i>n</i> -C ₈ H ₁₇ Br	15 min	98 ^c
	<i>n</i> -C ₈ H ₁₇ I	5 min	100 ^d
	<i>n</i> -C ₁₂ H ₂₅ Cl	10 h	89 ^e
	<i>n</i> -C ₁₂ H ₂₅ Br	30 min	100
	PhCH ₂ Cl	15 min	100
	cyclo-C ₃ H ₁₁ Br	90 min	90
	<i>n</i> -PrCH(Me)Br	2 h	94
	<i>n</i> -C ₆ H ₁₃ CH(Me)Br	5 h	90
	<i>n</i> -C ₆ H ₁₃ CH(Me)I	20 min	100
	CH ₂ Br ₂	15 min	95
<i>t</i> -BuSH	<i>n</i> -BuBr	15 min	92
	<i>n</i> -C ₈ H ₁₇ Br	15 min	96
	<i>n</i> -C ₁₆ H ₃₃ Br	15 min	95
	PhCH ₂ Cl	15 min	97
<i>n</i> -C ₈ H ₁₇ SH	<i>n</i> -BuBr	15 min	98
	<i>n</i> -C ₈ H ₁₇ Br	15 min	100
	PhCH ₂ Cl	15 min	100
	CH ₂ Br ₂	15 min	95
<i>n</i> -C ₁₂ H ₂₅ SH	<i>iso</i> -PrBr	3 h	97
	CH ₂ =CHCH ₂ Cl	90 min/	94
	CH ₂ =CHCH ₂ Br	30 min/	100
<i>n</i> -C ₁₆ H ₃₃ SH	<i>n</i> -BuBr	15 min	98
	PhCH ₂ Cl	15 min	100
PhCH ₂ SH	<i>n</i> -BuBr	15 min	98
	<i>n</i> -C ₈ H ₁₇ Br	15 min	100

^a 95% yield using 5 mmol TEBA-Cl over 30 min. ^b 87% yield using 5 mmol TEBA-Cl over 5 h. ^c 96% yield using 5 mmol TEBA-Cl over 30 min. ^d 100% yield using 5 mmol TEBA-Cl over 15 min. ^e 86% yield using 5 mmol TEBA-Cl over 10 h. ^f At room temperature.

TABLE 4.12
 One-pot synthesis of alkyl aryl trithiocarbonates

Thiol	Haloalkane	% yield	
		ArSCS.SR	ArSR
PhSH	PhCH ₂ Br	65	25
	EtI	57	32
	EtBr	40	29
	<i>n</i> -PrI	56	41
	<i>n</i> -PrBr	29	18
	<i>iso</i> -PrBr ^a	39	16
	<i>n</i> -BuBr ^a	41	38
	<i>n</i> -C ₅ H ₁₁ Br	39	51
	<i>iso</i> -C ₅ H ₁₁ Br	38	40
	<i>n</i> -C ₆ H ₁₃ Br	39	48
	<i>n</i> -C ₈ H ₁₇ Br	40	48
2-MeC ₆ H ₄ SH	MeI	61	22
3-MeC ₆ H ₄ SH	MeI	51	37
4-MeC ₆ H ₄ SH	MeI	72	22
4-ClC ₆ H ₄ SH	PhCH ₂ I	85	10
	MeI	24	44

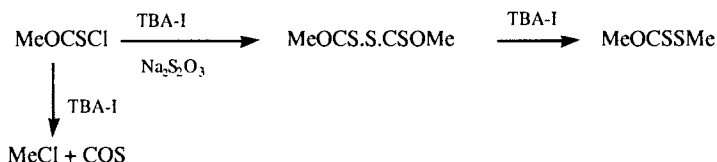
^a reaction time 24 h.

Cyclic trithiocarbonates are conveniently prepared by the phase-transfer catalysed reaction of 1,2- and 1,3-dichloro- and dibromoalkanes with sodium trithiocarbonate [47]. Diodoalkanes produce alkenes.

4.1.19 Cyclic trithiocarbonates

Aqueous Na₂CS₃ (30%, 3 ml) and Adogen (36 mg, 0.08 mmol) are added to the α,ω -dihaloalkane (2 mmol) in PhH (5 ml) and the mixture is stirred at 60°C for 8 h. The PhH solution is washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the cyclic trithiocarbonate, which can be purified by chromatography from silica [e.g. 58% from Cl(CH₂)₂Cl; 97% from Br(CH₂)₂Br; 81% from CH₃CHBrCH₂Br; 38% from Br(CH₂)₃Br; 66% from CH₃CHBr(CH₂)₂Br].

An unusual reaction of methoxythiocarbonyl chloride with tetra-*n*-butylammonium iodide in the presence of sodium thiosulphate leads to the formation of *O,S*-dimethyl dithiocarbonate [49]. The reaction appears to involve a reduction step, with the iodide anion being regenerated from the released iodine by the thiosulphate ions (Scheme 4.7). In the absence of the thiosulphate ions, the thiocarbonyl chloride decomposes to yield chloromethane and carbonyl sulphide.



Scheme 4.7

4.1.20 Reaction of methoxythiocarbonyl chloride with iodide ions

Aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2M, 200 ml) is added to MeOCSCl (50 g) and TBA-I (1.0 g, 2.7 mmol) in CH_2Cl_2 (200 ml) and the mixture is shaken until the reaction is complete. The organic phase is separated, washed with H_2O (2×50 ml), dried (Na_2SO_4), and evaporated to give *O,S*-dimethyl dithiocarbonate (74%).

In a one-pot synthesis of thioethers, starting from potassium *O*-alkyl dithiocarbonate [36], the base hydrolyses of the intermediate dialkyl ester, and subsequent nucleophilic substitution reaction by the released thiolate anion upon the unhydrolysed *O,S*-dialkyl ester produces the symmetrical thioether. Yields from the *O*-methyl ester tend to be poor, but are improved if cyclohexane is used as the solvent in the hydrolysis step (Table 4.13). In the alternative route from the *S,S*-dialkyl dithiocarbonates, hydrolysis of the ester in the presence of an alkylating agent leads to the unsymmetrical thioether [39] (Table 4.14). The slow release of the thiolate anions in both reactions makes the procedure socially more acceptable and obviates losses by oxidation.

TABLE 4.13

One-pot synthesis of unsymmetrical thioethers via *O,S*-dialkyl dithiocarbonates

Alkylating agent	Method	% yield
<i>From potassium O-ethyl dithiocarbonate</i>		
<i>n</i> -C ₈ H ₁₇ Br	4.1.21.A	80 ^a
<i>n</i> -C ₈ H ₁₇ I	4.1.21.A	85 ^b
<i>n</i> -C ₈ H ₁₇ OMes	4.1.21.A	80
<i>n</i> -C ₈ H ₁₇ OTos	4.1.21.A	83
<i>n</i> -C ₁₀ H ₂₁ Br	4.1.21.A	80
<i>n</i> -C ₁₆ H ₃₃ Br	4.1.21.A ^c	73
PhCH ₂ Cl	4.1.21.A	71
<i>From potassium O-methyl dithiocarbonate</i>		
<i>n</i> -C ₈ H ₁₇ Br	4.1.21.B	70 ^a
<i>n</i> -C ₁₂ H ₂₅ Br	4.1.21.B	73
<i>n</i> -C ₁₆ H ₃₃ Br	4.1.21.B	72
<i>From potassium O-n-octyl dithiocarbonate</i>		
MeI	4.1.21.A	34 ^{a,b}
EtI	4.1.21.A	47 ^{a,b}
<i>iso</i> -PrBr	4.1.21.A	60 ^a
<i>n</i> -C ₁₀ H ₂₁ Br	4.1.21.A	86
<i>From potassium O-n-decyl dithiocarbonate</i>		
EtI	4.1.21.A	37 ^b
<i>n</i> -C ₈ H ₁₇ Br	4.1.21.A	85
<i>From potassium O-iso propyl dithiocarbonate</i>		
<i>n</i> -C ₈ H ₁₇ Br	4.1.21.A ^d	25

^a (*n*-C₈H₁₇)₂S also detected. ^b The presence of the released iodide ion interferes with the second step of the reaction. The organic phase containing the ester should be separated, washed with H_2O (2×25 ml) before addition of a further amount of the catalyst (1.68 g) and KOH. ^c Reaction time 1 h. ^d Reaction time 90 min.

TABLE 4.14

Selected examples of unsymmetrical thioethers from *S,S*-dialkyl dithiocarbonates

Alkylating agent	Reaction time	% yield
<i>From S,S-dimethyl dithiocarbonate</i>		
<i>n</i> -C ₈ H ₁₇ Cl	45 min	100
<i>n</i> -C ₈ H ₁₇ Br	15 min	100
<i>n</i> -C ₈ H ₁₇ I	15 min	100
<i>n</i> -C ₈ H ₁₇ OMes	15 min	100
<i>n</i> -C ₈ H ₁₇ OTos	15 min	100
PhCH ₂ Cl	15 min	93
<i>n</i> -C ₆ H ₁₃ CH(Me)Br	1 h	94
4-NO ₂ C ₆ H ₄ Cl	15 min	100
4-MeCOC ₆ H ₄ Cl	3 h	100
2-Chlorobenzimidazole	15 min	100
<i>From S,S-diethyl dithiocarbonate</i>		
<i>n</i> -C ₈ H ₁₇ Br	30 min	100
<i>From S,S-di-n-butyl dithiocarbonate</i>		
<i>n</i> -C ₈ H ₁₇ Br	1.5 h	100
<i>From S,S-di-n-octyl dithiocarbonate</i>		
<i>n</i> -C ₈ H ₁₇ Br	3 h	100
<i>From S,S-dibenzyl dithiocarbonate</i>		
<i>n</i> -C ₈ H ₁₇ Cl	3 h	97
<i>n</i> -C ₈ H ₁₇ Br	30 min	97

4.1.21 One-pot synthesis of thioethers from potassium *O*-alkyl dithiocarbonate

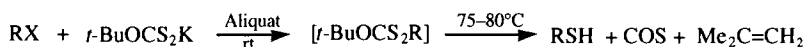
Method A: The *O,S*-dialkyl dithiocarbonate is prepared by procedure 4.1.14 from *O*-alkyl potassium dithiocarbonate (50 mmol). The mixture is cooled to 50°C and, without isolation of the ester, KOH pellets (14 g, 0.25 mol) are added portionwise at <80°C. The mixture is stirred at 80°C until GLC analysis indicates the complete disappearance of the ester (*ca.* 30 min). Petroleum ether (b.p. 40–60°C, 150 ml) is added and the organic phase is separated, dried (Na₂SO₄), filtered through silica, and fractionally distilled to give the thioether.

Method B: The alkylating agent (52 mmol) is added to MeOCS₂K (7.6 g, 52 mmol) and Aliquat (1.68 g, 4 mmol) in H₂O (50 ml), and the mixture is stirred at room temperature for 30 min. cyclo-C₆H₁₂ (50 ml) is added, followed by KOH pellets (14 g, 0.25 mol) with vigorous stirring. The mixture is heated at 70°C for 30 min and the thioether is isolated by the procedure described in 4.1.21.A.

4.1.22 Synthesis of unsymmetrical thioethers from *S,S*-dialkyl dithiocarbonates

The haloalkane (20 mmol), *S,S*-dialkyl dithiocarbonate (11 mmol) and TBA-Br (0.05 g, 0.15 mmol) in aqueous KOH (30%, 10 ml) are stirred under reflux (Table 4.14). The cooled mixture is extracted with Et₂O (3 × 50 ml) and the combined extracts are washed with H₂O (3 × 50 ml), dried (Na₂SO₄), and evaporated under reduced pressure to yield the thioether.

As indicated above, the traditional base-catalysed hydrolysis of *O,S*-dialkyl thio-carbonates for the synthesis of thiols is generally unsatisfactory, as oxidation leads to the formation of disulphides. Under phase-transfer conditions, the procedure produces thioethers to the virtual exclusion of the thiols, as a result of the slow release of the thiolate anions in the presence of the electrophilic ester. However, a simple modification of the reaction conditions provides an efficient one-pot reaction [50] from haloalkanes (Table 4.15) via the intermediate formation of the thermally labile *O-tert*-butyl-*S*-alkyl dithiocarbonates (Scheme 4.8).



Scheme 4.8

TABLE 4.15

Selected syntheses of thiols via *S*-alkyl *O-tert*-butyl dithiocarbonates

Haloalkane	Method	% yield of thiol
<i>n</i> -C ₈ H ₁₇ Cl	4.1.23.B	65
<i>n</i> -C ₈ H ₁₇ Br	4.1.23.A	87
<i>n</i> -C ₁₀ H ₂₁ Br	4.1.23.A	88
<i>n</i> -C ₁₂ H ₂₅ Cl	4.1.23.B	60
<i>n</i> -C ₁₂ H ₂₅ Br	4.1.23.A	91
<i>n</i> -C ₁₆ H ₃₃ Br	4.1.23.A	87
PhCH ₂ Cl	4.1.23.A	82
Br(CH ₂) ₄ Br	4.1.23.A	65
<i>n</i> -C ₅ H ₁₁ CH(CH ₃)Br	4.1.23.B	72
<i>n</i> -C ₆ H ₁₃ CH(CH ₃)Br	4.1.23.B	78

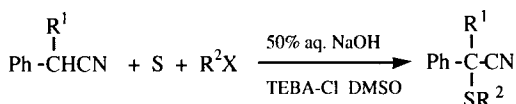
4.1.23 One-pot synthesis of thiols from potassium *O-tert*-butyl dithiocarbonate

Method A: The haloalkane (50 mmol), *t*-BuOCS₂K (10.3 g, 55 mmol) and Aliquat (1.5 g, 3.75 mmol) in H₂O (50 ml) are stirred until a yellow oil is produced (*ca.* 10–15 min). The temperature of the mixture is then raised to 75–80°C over a period of 10 min and maintained at this temperature until the evolution of gas ceases. The mixture is cooled, and petroleum ether (100 ml) is added. The organic phase is separated, washed with H₂O (2 × 20 ml), dried (MgSO₄), filtered through silica, and fractionally distilled to give the thiol.

Method B: The haloalkane (50 mmol) and Aliquat (1.5 g, 3.75 mmol) in H₂O are heated to *ca.* 50°C and *t*-BuOCS₂K (16.9 g, 90 mmol for *sec*-bromides and 28.2 g, 150 mmol for chlorides) is added in small portions over a period of 1 h (2 h for the chlorides) allowing the aqueous phase to become colourless before the next addition. The mixture is stirred for *ca.* 30 min and the temperature of the system is then raised to 75–80°C and the thiols are isolated as described in 4.1.23.A.

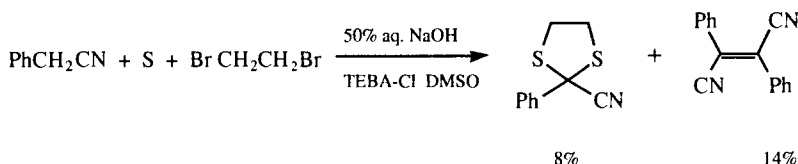
Thioethers have also been prepared by the direct reaction of sulphur with stabilized carbanions in the presence of an alkylating agent (Scheme 4.9). The overall

reaction is catalysed by quaternary ammonium salts, and the addition of dimethyl sulphoxide is advantageous for high yields [51] (Table 4.16). A major side reaction produces polysulphides and, in the absence of dimethyl sulphoxide, the yields of the thioethers are generally low (*ca.* 10%).



Scheme 4.9

Under similar conditions, phenylacetonitrile reacts with sulphur and 1,2-dibromoethane to produce, in low yield, the thioacetal together with the dicyanostilbene [51] (Scheme 4.10).



Scheme 4.10

TABLE 4.16

Formation of thioethers from phenylacetonitriles, sulphur and haloalkanes

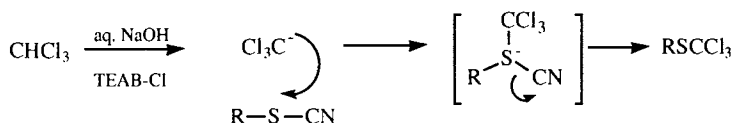
PhCH(CN)R	Haloalkane	% yield
R = Me	MeBr	72
CH ₂ =CHCH ₂	<i>n</i> -BuCl	71
<i>iso</i> -Pr	<i>n</i> -BuCl	63
Ph	MeBr	49 ^a

^a Ph₂C(CN)C(CN)Ph₂ (21%) also isolated.

4.1.24 Direct reaction of sulphur with carbanions to form thioethers

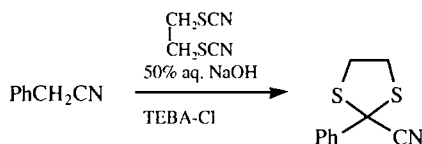
The haloalkane (67 mmol) is added to a stirred mixture of the phenylacetonitrile (20 mmol), sulphur (1.0 g, 31 mmol), TEBA-Cl (0.1 g, 0.4 mmol), and DMSO (1.0 ml) in aqueous NaOH (50%, 10 ml) at 45 °C. The exothermic reaction mixture is stirred for 75 min and then diluted with H₂O (25 ml) and extracted with PhH (2 × 25 ml). The organic extracts are dried (MgSO₄) and fractionally distilled to yield the thioether.

In the unconventional synthesis of thioethers (Scheme 4.11), cyanide ion is displaced from thiocyanates by carbanions [52, 53], which have been generated under phase-transfer catalytic conditions (*cf.* 4.1.12). Thiocyanates are readily obtained by a standard catalysed nucleophilic substitution reaction [4, 54–58] (see Table 4.19). Aryl thiocyanates are obtained from activated aryl halides [4, 57] (see Chapter 2).



Scheme 4.11

In the reaction of the phenylacetonitrile carbanion with thiocyanates, a major side reaction leads to the formation of the dialkyl disulphides, as a result of the base-catalysed decomposition of the thiocyanate. This side reaction is reported to be insignificant in the reactions of the other carbanions. Phenylacetonitrile reacts with 1,2-ethanyl bithiocyanate to produce 2-cyano-2-phenyl-1,3-thiolanes [52] under conditions analogous to those used for the synthesis of the thioethers (Scheme 4.12).



Scheme 4.12

4.1.25 Liquid:liquid two-phase synthesis of thiocyanates

Method A: The haloalkane (0.14 mol) is added to KSCN (28 g, 0.29 mol) and TBA-Br or Aliquat (1.2 mmol) in H_2O (30 ml) and the mixture is stirred under reflux (Table 4.17). The mixture is cooled to room temperature and the organic phase is separated, dried (MgSO_4), and distilled under reduced pressure to yield the thiocyanate.

Method B: The haloalkane (0.1 mol) is added to a stirred solution of NaSCN (1.0 g, 0.12 mol) and TEBA-Cl (27.4 g, 0.12 mol) in H_2O (50 ml) at 35°C . The two-phase system is stirred at 90°C for 4–5 h and then cooled to room temperature. The mixture is extracted with Et_2O (2×25 ml) and the extracts are washed with brine (2×25 ml), dried (CaCl_2), and evaporated to yield the thiocyanate.

4.1.26 Solid:liquid two-phase synthesis of thiocyanates

The haloalkane in MeCN is added to an excess of finely powdered KSCN and 1% molar equivalent of Aliquat. The mixture is stirred at room temperature for *ca.* 2 h, filtered, and the filtrate is fractionally distilled under reduced pressure to produce the thiocyanate (>95%).

4.1.27 Synthesis of thioethers from alkyl thiocyanates (Table 4.18)

Method A: The alkyl thiocyanate (0.15 mol) is added with stirring to $\text{PhC}\equiv\text{CH}$ (15.3 g, 0.15 mol) and TEBA-Cl (0.23 g, 1 mmol) in aqueous NaOH (50%, 25 ml) at 35°C . The mixture is stirred for 5 h and then poured into H_2O (50 ml) and extracted with CH_2Cl_2 (3×25 ml). The organic extracts are washed with H_2O (25 ml), dried (MgSO_4), and fractionally distilled under reduced pressure to yield the thioether.

TABLE 4.17
 Liquid-liquid two-phase synthesis of thiocyanates

Alkylating agent	Reaction time	% yield
EtBr	20 h	99
EtI	3 h	99
<i>n</i> -PrBr	48 min	100
<i>n</i> -BuCl	12 h	100
<i>n</i> -BuBr	1 h	99
<i>n</i> -BuI	2.5 h	96
<i>n</i> -C ₅ H ₁₁ Br	1 h	100
<i>n</i> -C ₆ H ₁₃ Br	48 min	99
<i>n</i> -C ₇ H ₁₅ Br	1 h	100
<i>n</i> -C ₈ H ₁₇ Br	48 min	100
<i>n</i> -C ₁₀ H ₂₁ Br	72 min	99
PhCH ₂ Cl	30 min	88
MeCHBrEt	2 h	94
<i>n</i> -PrCHBrMe	2.5 h	100

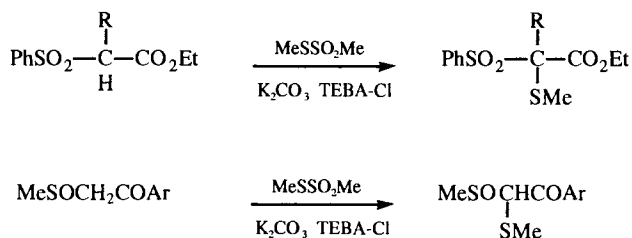
Method B: Aqueous NaOH (50%, 40 ml) is added dropwise to a stirred solution of the alkyl thiocyanate (0.2 mol) and TEBA-Cl (0.5 g, 2.2 mol) in CHCl₃ (79 g, 0.6 mol). The temperature of the slightly exothermic reaction rises to *ca.* 40°C and this temperature is held for *ca.* 3–4 h. The mixture is poured into H₂O (50 ml) and the organic phase is separated, washed with H₂O (2 × 25 ml), dried (MgSO₄), and evaporated to yield the thioether.

Method C: Aqueous NaOH (50%, 15 ml) is added to a stirred mixture of 2-phenyl propionitrile (13.1 g, 0.1 mol), TEBA-Cl (0.2 g, 1 mmol), and the alkyl thiocyanate (0.2 mol) at 50°C. The mixture is stirred for 4 h at 50°C and the thioether is isolated by the procedure described in 4.1.27.A.

 TABLE 4.18
 Selected examples of the conversion of thiocyanates into thioethers

RSCN	Method	% yield of thioether
<i>Reaction with phenylethyne</i>		
R = Me	4.1.27.A	35
Et	4.1.27.A	42
<i>n</i> -C ₅ H ₁₁	4.1.27.A	45
<i>Reaction with chloroform</i>		
Me	4.1.27.B	61
Et	4.1.27.B	64
<i>n</i> -Pr	4.1.27.B	67
<i>n</i> -C ₅ H ₁₁	4.1.27.B	86
PhCH ₂	4.1.27.B	80
(CH ₂) ₃ Cl	4.1.27.B	77
(CH ₂) ₃ CN	4.1.27.B	70
Ph	4.1.27.B	60
<i>From 2-phenylpropionitrile</i>		
Et	4.1.27.C	77
<i>n</i> -C ₅ H ₁₁	4.1.27.C	68

Direct sulphonylation of activated methylene groups to form methyl thioethers is possible under basic conditions, when the stabilized carbanion reacts with *S*-methyl methanethiosulphonate. The reaction has been applied successfully in, for example, reactions with β -keto sulfoxides [59] and α -sulphonyl acetic esters [60] (Scheme 4.13).



Scheme 4.13

4.1.28 Sulphonylation of activated methylene groups (Table 4.19)

The activated methylene compound (2 mmol), TEBA-Cl (46 mg, 0.2 mmol) and powdered K_2CO_3 (0.55 g) in CH_2Cl_2 or PhH (10 ml)* are stirred at room temperature for *ca.* 1 h. MeSSO_2Me (0.25 g, 2 mmol) in CH_2Cl_2 (3 ml) is added, and the mixture is stirred for 2–6 h and then filtered. The solid is washed with CH_2Cl_2 (20 ml) and the combined solutions are washed with H_2O (2×20 ml), dried (MgSO_4), and evaporated to yield the methyl thioether (* a 1 : 1 mixture of CH_2Cl_2 and PhH is preferred for the β -keto sulfoxides).

A procedure, which has been used successfully for the synthesis of dialkyl thioethers from thioacetamide has been extended to the preparation of a range of *S*-alkyl thiocarboxylic esters [35] (Table 4.20). The intermediate *S*-acyl ethaniminium salt (Scheme 4.14) is not stable and is converted directly into the *S*-alkyl thioester. The choice of catalyst affects the yield of the thioesters. Thus, *S*-*n*-octyl thiobenzoate

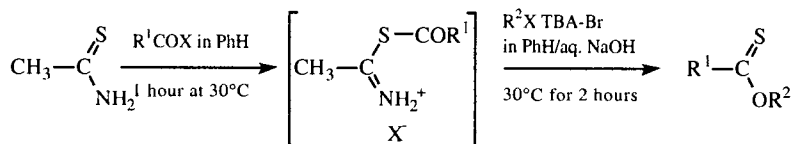
TABLE 4.19
Sulphonylation of activated methylene groups

Substrate	Reaction conditions	% yield
<i>PhSO₂CHRCO₂Et</i>		
R = H	4.1.28/2 h	75
Me	4.1.28/2 h	92
Ph	4.1.28/6 h	79
<i>RCOCH₂SOMe</i>		
R = Ph	4.1.28/2 h	67
4-ClC ₆ H ₄	4.1.28/2 h	45
4-MeC ₆ H ₄	4.1.28/2 h	45
4-MeOC ₆ H ₄	4.1.28/2 h	65

TABLE 4.20
S-Alkyl thiocarboxylic esters from thioacetamide

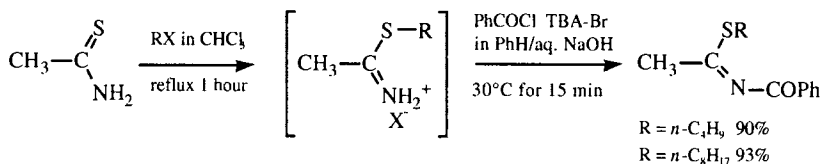
Acyl halide	Haloalkane	% yield of thioester
<i>n</i> -C ₃ H ₇ COCl	<i>n</i> -C ₈ H ₁₇ Br	89
<i>n</i> -C ₅ H ₁₁ COCl	PhCH ₂ Br	86
<i>n</i> -C ₇ H ₁₅ COCl	PhCH ₂ Br	86
<i>t</i> -C ₄ H ₉ COCl	<i>n</i> -C ₈ H ₁₇ Br	83
PhCOBr	<i>n</i> -C ₄ H ₉ Br	91
PhCOBr	<i>n</i> -C ₈ H ₁₇ Br	87
PhCOBr	CH ₃ CH=CHCH ₂ Br	88
PhCOBr	PhCH ₂ Br	82
4-MeOC ₆ H ₄ COCl	<i>n</i> -C ₈ H ₁₇ Br	95
4-NO ₂ OC ₆ H ₄ COCl	<i>n</i> -C ₈ H ₁₇ Br	63
PhCH=CHCOCl	PhCH ₂ Br	93

is obtained in yields of 87%, 71%, and 3%, respectively, when the reaction is catalysed by tetra-*n*-butylammonium bromide, Aliquat, and benzyltriethylammonium chloride. No thioester is obtained in the absence of the catalyst; only thiobenzoic acid (85%) is isolated.



Scheme 4.14

The 'reverse' reaction in which thioacetamide is initially alkylated and then reacted under phase-transfer catalytic conditions with the acyl halide results in the formation of *N*-acylthioamides (Scheme 4.15), with only trace amounts of the *S*-alkyl thioesters [35]. *S*-Alkyl thioacetates have also been obtained from trifluoromethylsulphonyloxy compounds upon reaction with potassium thioacetate in the presence of TDA-1 [61]. It is probable that tetraalkylammonium salts would be equally good catalysts.



Scheme 4.15

S-Alkyl thiocarbonates (55–90%) are also obtained using polymer supported catalysts (Table 4.21) [62].

TABLE 4.21
S-Alkylation of the thioacetate anion using Amberlyst A-26 resin

Haloalkane	Reaction conditions	% yield of thioester
<i>n</i> -C ₈ H ₁₇ Br	4.1.31 / <i>n</i> -C ₆ H ₁₄ /rt/2 h	90
<i>n</i> -C ₈ H ₁₇ Cl	4.1.31 / <i>n</i> -C ₆ H ₁₄ /reflux/3 h	92
<i>n</i> -C ₈ H ₁₇ OTos	4.1.31 /THF/reflux/20 h	69
<i>n</i> -C ₈ H ₁₇ OTos	4.1.31 /PhH/reflux/4 h	95
<i>n</i> -C ₁₈ H ₃₇ OTos	4.1.31 /PhH/reflux/6 h	95
Br(CH ₂) ₄ Br	4.1.31 / <i>n</i> -C ₆ H ₁₄ /rt/2 h	96
PhCH ₂ Br	4.1.31 / <i>n</i> -C ₆ H ₁₄ /rt/3 h	87
CH ₂ =CHCH ₂ Br	4.1.31 /Et ₂ O/rt/3 h	56
<i>n</i> -C ₆ H ₁₁ CH(Me)Br	4.1.31 / <i>n</i> -C ₆ H ₁₄ /reflux/3 h	90
cyclo-C ₆ H ₁₁ Br	4.1.31 /PhH/reflux/10 h	62
ClCH ₂ CO ₂ Et	4.1.31 / <i>n</i> -C ₆ H ₁₄ /rt/3 h	85
PhCOCH ₂ Br	4.1.31 /Et ₂ O/rt/5 h	80

4.1.29 S-Alkyl thiocarboxylic esters from thioacetamide

Thioacetamide (1.83 g, 30 mmol) and the acyl halide (30 mmol) in PhH (50 ml) are stirred under N₂ at room temperature for 3 h to give the unstable *S*-acyl ethaniminium salt, which is not isolated. The haloalkane (30 mmol), TBA-Br (0.29 g, 0.9 mmol) and aqueous NaOH (10%, 50 ml) are added and the mixture stirred for 2 h at 30°C. The organic phase is separated, washed with H₂O (3 × 50 ml), dried (Na₂SO₄), and evaporated to give the thioester.

4.1.30 *N*-Acylthioamides from thioacetamide

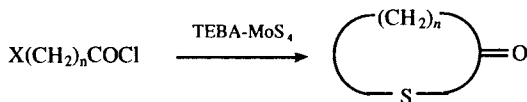
The *S*-alkylthioethaniminium salt (10 mmol) (see **4.1.11**) and the appropriate acyl halide (10 mol) in PhH (50 ml) are stirred at room temperature with TBA-Br (97 mg, 0.3 mmol) in aqueous NaOH (30%, 50 ml) for 15 min. The organic phase is separated, washed with H₂O (3 × 50 ml), dried (Na₂SO₄), and fractionally distilled under reduced pressure to give the thioamide.

4.1.31 *S*-Alkyl thioacetates

The alkylating agent (4 mmol) is stirred with Amberlyst A-26 (MeCS₂ form) (1.5 g) in the solvent (20 ml) indicated in Table 4.21. The mixture is filtered and the resin is washed with Et₂O (2 × 50 ml). The filtrate and washings are fractionally distilled under reduced pressure to yield the thioacetate.

Bis-acyl sulphides are obtained in only low yield by the standard reaction of sodium sulphide with an acyl chloride, but the addition of Adogen results in their viable synthesis with yields >70%. Examples using quaternary phosphonium salts provide the optimum yields (> 90%) [63]. Similarly, thiophenols have been benzoylated using benzoyl chloride under basic conditions in the presence of ammonium salts [12].

An interesting C-S bond formation mediated by benzyltriethylammonium tetrathiomolybdate converts ω -halo acid chlorides into thiolactones [64] (Scheme 4.16).



Scheme 4.16

4.1.32 Thiolactones from ω -halo acid chlorides

Method A: TEBA-MoS₄ (1.56 g, 2.6 mmol) in CHCl₃ (15 ml) is added dropwise with stirring to the ω -halo acid chloride (2.4 mmol) at -10°C. The mixture is stirred for 4–24 h at 0°C, the solvent is evaporated and the residue taken up in CH₂Cl₂:Et₂O (1 : 5, 30 ml). The solution is filtered and evaporated to give the thiolactone, which can be purified by chromatography (e.g. halogen, n, reaction time, yield: I, 2, 4 h, 30%; Br, 3, 5 h, 65%; Br, 4, 7 h, 77%; Br, 5, 24 h at 25°C, 13%).

Method B: The ω -iodo acid chloride (2 mmol) is added to the solid TEBA-MoS₄ (1.34 g, 2.2 mmol) and the mixture is ground together for 15 min. The thiolactone is extracted from the solid mass with CH₂Cl₂ and purified by chromatography from silica ($n = 3$, 52%; $n = 4$, 70%).

S-Alkynyl phosphorodithionates have been prepared in high yield by the nucleophilic displacement of iodobenzene from alkynyl phenyl iodonium salts [65].

4.1.33 O,O-Dialkyl S-alkynyl phosphorodithionates

The iodonium salt, RC≡C⁺Ph (1 mmol) in CHCl₃ (15 ml) is stirred with the potassium O,O-dialkyl phosphorodithionate, (R'O)₂PS.SK, (1.5 mmol) and TEBA-Cl (23 mg, 0.1 mmol) in H₂O (15 ml) at room temperature for 15–30 min. The aqueous phase is separated, extracted with CHCl₃ (3 × 10 ml), and the combined organic solutions are washed with H₂O (3 × 20 ml), dried (MgSO₄), and evaporated to yield the alkynyl phosphorodithionate, (R'O)₂PS.SC≡CR (e.g. R = Ph: R' = Me, 85%; Et, 83%; PhCH₂, 91%; Ph, 93%. R = *t*-Bu: R' = Et, 94%; PhCH₂, 89%; Ph, 95%).

The reductive formation of C-S bonds via the reaction of carboxylic acids with phosphorus pentasulphide and red phosphorus has been utilized in the synthesis of 3-arylthiophenes starting from 2-arylsuccinic acids [66, 67]. The reaction is catalysed by benzyltriethylammonium chloride, but it has been suggested that co-catalysis with 18-crown-6 is advantageous [67].

4.1.34 3-Arylthiophenes

Disodium 2-arylsuccinate (20 mmol), P₂S₅ (6.66 g, 30 mmol), red phosphorus (2.48 g, 80 mmol) and TEBA-Cl (0.23 g, 1 mmol) in 1,2-Cl₂C₆H₄ (50 ml) are heated with stirring

at 130–135 °C for 6–7 h. The mixture is evaporated under reduced pressure and CHCl_3 (20 ml) and H_2O (20 ml) are added to the residue. The pH of the mixture is adjusted to *ca.* 7.0 by the addition of aqueous NaOH (10%) and the aqueous phase is then separated and extracted with CHCl_3 (2×15 ml). The combined CHCl_3 solutions are washed well with H_2O , dried (Na_2SO_4), and evaporated. Chromatography of the crude product on silica yields the 3-arylthiophene (e.g. Ph, 80%; 4-MeC₆H₄, 85%; 4-MeOC₆H₄, 80%; 4-ClC₆H₄, 82%). Yields can be improved by *ca.* 15% on the addition of 18-crown-6 (0.32 g, 1.2 mmol).

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4.2 MICHAEL-TYPE REACTIONS OF THIOLS WITH ELECTRON-DEFICIENT C=C AND C≡C BONDS

The base-catalysed addition of thiols to π -electron-deficient alkenes is an important aspect of synthetic organic chemistry. Particular use of Triton-B, in place of inorganic bases, has been made in the reaction of both aryl and alkyl thiols with 1-acyloxy-1-cyanoethene, which behaves as a formyl anion equivalent in the reaction [1]. Tetra-*n*-butylammonium and benzyltriethylammonium fluoride also catalyse the Michael-type addition of thiols to α,β -unsaturated carbonyl compounds [2]. The reaction is usually conducted under homogeneous conditions in tetrahydrofuran, 1,2-dimethoxyethane, acetone, or acetonitrile, to produce the thioethers in almost quantitative yields (Table 4.22). Use has also been made of polymer-supported qua-

TABLE 4.22

Michael-type reactions of thiols with α,β -unsaturated carbonyl compounds $R^1R^2C=CHCOR^3$

Thiol	$R^1R^2C=CHCOR^3$			Reaction conditions ^a	% yield of thioether
	R^1	R^2	R^3		
PhSH	H	H	OMe	4.2.1/TBA-Br/10 min	99
	Me	H	OMe	4.2.1/TEBA-Cl/15 h	83
	H	H	Me	4.2.1/TBA-Br/1 h	98
	Me	Me	Me	4.2.1/TBA-Br/5 h	94
	<i>n</i> -Pr	H	H	4.2.1/TBA-Br/10 min	96
	Ionone			4.2.1/TEBA-Cl/7 days ^b	87
	Angelicone			4.2.1/TEBA-Cl/18 h	96
PhCH ₂ SH	H	H	OMe	4.2.1/TBA-Br/20 h	87
	Me	H	OMe	4.2.1/TEBA-Br/20 min ^b	100
	Me	Me	Me	4.2.1/TEBA-Br/2 h	93
	<i>n</i> -Pr	H	H	4.2.1/TBA-Br/10 days	79
HSCH ₂ CO ₂ Et	H	H	OMe	4.2.1/TBA-Br/7 h	95
	Me	Me	Me	4.2.1/TBA-Br/2 days	80

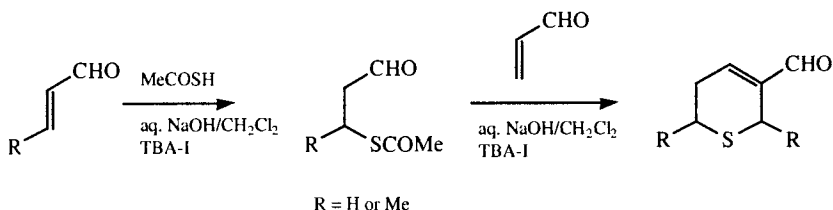
^a in THF, ^b in Me₂CO.

ternary ammonium salts [3]. Tetra-*n*-butylammonium alkyl and arylthiolates have been reported to initiate anionic polymerization of alkyl acrylates in a range of solvents to produce isotactic polymers with narrow molecular weight distributions [4].

The importance of chiral thiols and thioether linkages in biological systems has prompted intense investigation of the use of chiral amines [see e.g. 5–11] and ammonium salts [see e.g. 12] as agents for asymmetric induction in the Michael-type addition reaction. Considerable success has been achieved using chinchona alkaloids and their *N*-alkyl derivatives (see Chapter 12).

4.2.1 Conjugate addition of thiols to α,β -unsaturated carbonyl compounds

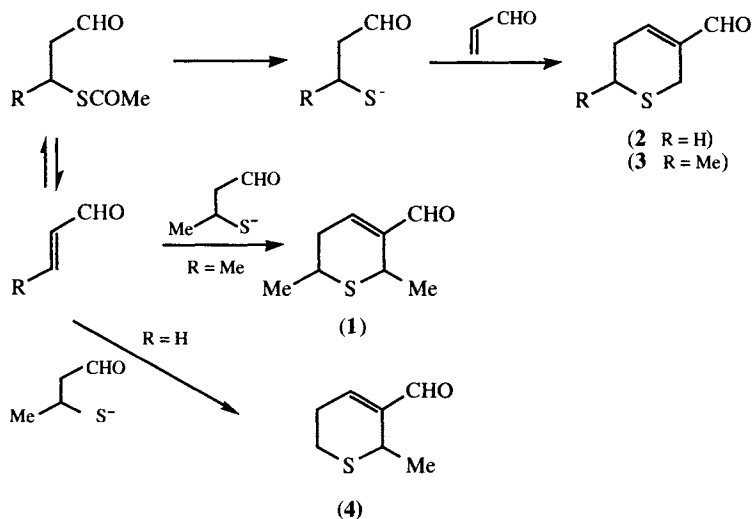
The thiol (5 mmol) and the conjugated carbonyl compound (5 mmol) in THF (5 ml) is added to the catalyst (0.1 mmol) under N₂ and the mixture is stirred at 20–25°C (Table 4.22). *n*-C₆H₁₄ (50 ml) is added, the mixture is filtered, and the filtrate is fractionally distilled to yield the adduct.



Scheme 4.17

The analogous two-phase reaction of acrolein with thiolacetic acid under basic conditions in the presence of tetra-*n*-butylammonium iodide initially forms the Michael adduct which, upon hydrolysis, reacts further to produce 1-formyl-5-thia-cyclohexene (see Scheme 4.17). In a similar manner, crotonaldehyde produces 1-formyl-4,6-dimethyl-5-thiacyclohexene [13].

'Crossed' reactions of the two aldehydes under phase-transfer catalytic conditions with the intermediate thioacetates, which can be isolated under controlled reaction conditions [14], leads to the formation of three products [13], as result of retro-Michael reactions (Scheme 4.18). In the case of the reactions involving crotonaldehyde, the major product results from the reaction of the aldehyde with the released thiolacetic acid, with lesser amounts of the expected 'crossed' reaction products (Table 4.23). In contrast, the reaction of acrolein with the thioacetate derived from crotonaldehyde produces, as the major product, the 'crossed' cycloadduct. These observations reflect the relative stabilities of the thioacetates and the relative susceptibilities of acrolein and crotonaldehyde to the Michael reaction.



Scheme 4.18

Table 4.23

'Crossed' Michael-type reactions of thioacetates $MeCOSCH(R^1)CH_2CHO$ with α,β -unsaturated aldehydes $R^2CH=CHCHO$

Thioacetate	R ² CH=CHCHO Method		% yield of cycloadduct			
			1	2	3	4
R ¹ = Me ^a	R ² = H ^a	4.2.3.B (0 °C)	79	13	8	0
H ^a	Me ^a	4.2.3.A (0 °C)	23	23	0	54
H ^a	Me ^b	4.2.3.B (0 °C)	33	7	0	60
H ^a	Me ^a	4.2.3.B (20 °C)	29	10	0	61
H ^b	Me ^a	4.2.3.B (20 °C)	31	27	0	42

^a One equivalent. ^b Two equivalents.

4.2.2 Michael addition of thiolacetic acid to acrolein and crotonaldehyde

The unsaturated aldehyde (0.1 mol) is added to a two-phase system of thiolacetic acid (7.6, 0.1 mol) in aqueous NaOH (50%, 16 ml) and TBA-I (0.1 g, 0.27 mmol) in CH_2Cl_2 (100 ml) over a period of *ca.* 30 min at 0°C. The mixture is stirred for 2.5 h at 0°C and then heated under reflux for 20 min. The organic phase is separated, diluted with Et_2O (50 ml), washed with H_2O (3×25 ml), and dried (MgSO_4). Evaporation of the solvent gives 1-formyl-5-thiacyclohex-1-ene (41%) from acrolein and 1-formyl-4,6-dimethyl-5-thiacyclohex-1-ene (81%) from crotonaldehyde.

4.2.3 Reaction of thioacetates with α,β -unsaturated aldehydes

Method A: The thioacetate (0.1 mol) is added rapidly at 0°C to a vigorously stirred two-phase system of aqueous NaOH (5%, 15 ml): CH_2Cl_2 (100 ml) containing TBA-I (0.1 g, 0.27 mmol) and the mixture is stirred at 0°C for *ca.* 2 min. The α,β -unsaturated aldehyde (0.1 mol) is added rapidly and the exothermic reaction mixture is stirred, with external cooling, for *ca.* 15 h. The mixture is heated under reflux for 1 h and then cooled to room temperature. H_2O (100 ml) is added and the organic phase is separated. The aqueous phase is extracted with Et_2O (2×25 ml) and the combined organic solutions are washed with H_2O until neutral, dried (Na_2SO_4), and evaporated to yield the cycloadduct.

Method B: The above reaction conditions are used, except that the thioester and the unsaturated aldehyde are added simultaneously to the stirred and cooled solution of the base and catalyst.

Thiols react directly with non-activated alkynes [15] and with 1-alkynyl thioethers [16] to yield alkenyl thioethers in good yield (>76%), whereas thiocyanate anions only add to non-activated alkynes under acidic phase-transfer catalytic conditions on the addition of mercury(II) thiocyanate. Terminal alkynes are converted into vinyl thiocyanates, but disubstituted alkynes also form vinyl isothiocyanates [17]. Major by-products are the ketones formed by solvolysis of the alkynes.

4.2.4 Vinyl thioethers

MeSH (19.24 g, 0.4 mol) is bubbled through aqueous KOH (50%, 40 ml) at 0°C over 15 min, or EtSH (24.85 g, 0.4 mol) is added dropwise to the aqueous KOH. Aliquat (5 g, 12 mmol) is added followed by the alkyne (0.2 mol) and the mixture is stirred at 70°C for 30 min and then the upper brown phase is removed. The remaining mixture is heated at 90°C for *ca.* 30 min, then cooled and extracted with $n\text{-C}_5\text{H}_{12}$ (3×25 ml). The dried (MgSO_4) extracts are fractionally distilled to yield the thioether [e.g. $\text{MeC}\equiv\text{CSEt}$ gives $\text{MeC}(\text{SMe})=\text{CHSEt}$ (86%) and $\text{MeC}(\text{SEt})=\text{CHSEt}$ (76%); $\text{EtC}\equiv\text{CSMe}$ gives $\text{EtC}(\text{SMe})=\text{CHSMe}$ (88%) and $\text{EtC}(\text{SEt})=\text{CHSMe}$ (84%)].

4.2.5 Vinyl thiocyanates

The alkyne (0.1 mol) is added to conc. H_2SO_4 (96%, 10 ml) and TBA-SCN (0.1 mol), obtained from the reaction of TBA-Br with KSCN, in CH_2Cl_2 (100 ml), followed by $\text{Hg}(\text{SCN})_2$ (3.17 g, 0.01 mol). The mixture is stirred at 40°C for *ca.* 3 h and $n\text{-C}_5\text{H}_{12}$ is then added to precipitate the mercury and ammonium salts. The filtered solution is evaporated to yield the vinyl thiocyanate.

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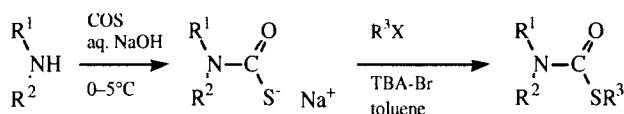
4.3 SYNTHESIS OF THIOAMIDES AND RELATED COMPOUNDS

S-Alkyl thiocarbamates (Table 4.24) have been synthesized [1] by a procedure (Scheme 4.19) which is closely analogous to that employed for the preparation of *S*-alkyl thiocarbonates (see Section 4.1). *S*-Glycosyl dithiocarbamates [2], which are useful precursors for thiosugars, have been prepared by simple nucleophilic displacement of the tosyloxy group by the *N,N*-diethylthiocarbamate anion (*cf.* preparation of *S*-glycosyl dithiocarbonates, **4.1.13**).

TABLE 4.24

Selected examples of the synthesis of *S*-alkyl thiocarbamates

Amine	Haloalkane	% yield
Et ₂ NH	PhCH ₂ Cl	93
	2-ClC ₆ H ₄ CH ₂ Cl	92
	4-ClC ₆ H ₄ CH ₂ Cl	95
	4-MeC ₆ H ₄ CH ₂ Cl	96
	PhCOCH ₂ Cl	62
	MeCOCH ₂ Cl	84
<i>iso</i> -Pr ₂ NH	PhCH ₂ Cl	91
	PhCOCH ₂ Cl	94
	MeCOCH ₂ Cl	85
	ClCH=C(Cl)CH ₂ Cl	91
	CH ₂ =C(Cl)CH ₂ Cl	90
	Cl ₂ C=C(Cl)CH ₂ Cl	92



Scheme 4.19

In a manner analogous to that used for the formation of *S*-alkyl thioacetates using a polymer-supported quaternary ammonium salt (**4.1.31**), the dithiocarbamate anion can be *S*-alkylated under mild conditions [3]. The corresponding arylation reaction with activated aryl systems requires more vigorous conditions:

4.3.1 Liquid:liquid two-phase synthesis of *S*-alkyl thiocarbamates

COS is bubbled through the amine (0.19 mol) and NaOH (8.4 g) in H₂O (34 ml) at 0–5 °C until there is an increase in weight of 11 g (*ca.* 30 min). The alkylating agent (0.16 mol) and TBA-Br (1.4 g, 4.4 mmol) in PhMe (27 ml) are added and the mixture is stirred at 20–30 °C for 2–3 h. The PhMe phase is separated, washed with H₂O (25 ml), dried (MgSO₄), and evaporated under reduced pressure to yield the thiocarbamate, which is purified by fractional distillation.

4.3.2 *S*-Glycosyl *N,N*-diethyldithiocarbamates

Et₃NCS₂Na·3H₂O (113 mg, 0.5 mmol) is added to the monosaccharide (0.5 mmol), TBA-Cl (35 mg, 0.125 mmol) and TosCl (133 mg, 0.7 mmol) in PhH (15 ml). Aqueous NaOH (50%, 5 ml) is added and the two-phase system is stirred at room temperature for *ca.* 2 h. The organic phase is separated, washed with H₂O (3 × 10 ml), dried (Na₂SO₄), and evaporated. The syrupy carbamate can be purified by chromatography from silica gel.

4.3.3 Polymer-supported synthesis of *S*-alkyl and *S*-aryl dithiocarbamates (Table 4.25)

Amberlyst A26 (in Cl[–] form) is exchanged twice with the aqueous sodium dithiocarbamate (sat. soln.), rinsed successively with H₂O, EtOH and Et₂O, and dried. The resin is stable for several days, when stored at room temperature. Alkylation is effected by shaking the resin with the appropriate alkylating agent in PhH at 20 °C.

The classical reaction of hydrogen sulphide with nitriles in basic media is catalysed by the addition of, for example, Aliquat or tetra-*n*-butylammonium bromide [4]. The reaction proceeds most rapidly with dilute aqueous solutions of sodium sulphide under 1–2 atmospheres of hydrogen sulphide to produce thioamides in good yields (>70%).

4.3.4 Synthesis of thioamides from nitriles (Table 4.26)

The nitrile (0.14–0.15 mol) in PhH (20 ml) is added to Na₂S·9H₂O (0.54 g, 2.5 mmol) and Aliquat (1.0 g, 2.5 mmol) in H₂O (20 ml). The reaction vessel is flushed with H₂S and then maintained under a pressure of *ca.* 2 atmos. while the reaction mixture is stirred at 70 °C. The mixture is then cooled to room temperature and the precipitated thioamide is collected, washed with H₂O, and recrystallized.

TABLE 4.25
Polymer-supported synthesis of alkyl dithiocarbamates $R_2NCS.SR^1$

Dithiocarbamate anion	Alkylating agent	% yield ^a
$Me_2NCS_2^-$	$PhCH_2Br$	96
	$HC\equiv CCH_2Br$	42
$Et_2NCS_2^-$	$PhCH_2Br$	82
	$HC\equiv CCH_2Br$	59
	$CH_2=CHCH_2Br$	61
	CH_3I_2	81
	$Br(CH_2)_2Br$	76
	$Br(CH_2)_3Br$	96
	$BrCH_2CH_2(OCH_2CH_2)_2Br$	90 ^b
	$BrCH_2CH_2(OCH_2CH_2)_3Br$	90 ^b
	$2,4-(NO_2)_2C_6H_3Cl$	81 ^c
	$PhN_2^+BF_4^-$	65 ^d
	$Ph_2I^+ I^-$	41 ^e
	2,4,6-Trichlorotriazine	65 ^f

^a 12 hours at 20°C. ^b 12 hours at 87°C. ^c 20 hours at 20°C. ^d 12 hours under reflux in *t*-AmOH. ^e in $n-C_6H_{12}/H_2O$. in PhH/CH_3CN .

TABLE 4.26
Selected examples of the synthesis of thioamides from nitriles

Nitrile	Reaction conditions	% yield
<i>n</i> -PrCN	4.3.4/8 h	46
$PhCH_2CN$	4.3.4/6 h	58 ^a
$PhCN$	4.3.4/2.5 h	98 ^b
4-MeC ₆ H ₄ CN	4.3.4/1 h	86
4-MeC ₆ H ₄ CN	4.3.4/1 h	86
4-ClC ₆ H ₄ CN	4.3.4/2 h	88
3-pyridylnitrile	4.3.4/4 h	97 ^c

^a Using 1.5 atmos. H₂S; 50% after 4 h using 2 atmos. H₂S. ^b Using 6.9 mmol Na₂S.9H₂O; 92% after 4 h using 2.5 mmol Na₂S.9H₂O. ^c Using 1 atmos. H₂S.

Symmetrical dialkyl and diaryl thioureas have been prepared in generally good yield (60–90%) from the reaction of the amine with thiophosgene, formed *in situ* from the catalysed reaction of carbon tetrachloride with sodium sulphide [5]. Reaction with diamines yields cyclic ureas.

4.3.5 *N,N'*-Disubstituted thioureas

The amine (60 mmol) in CCl_4 (50 ml) is added to TEBA-Cl (0.36 g, 1.6 mmol) and Na₂S (64 mmol) in H₂O (20 ml). The exothermic reaction is stirred at room temperature for 8 h, then poured into H₂O (100 ml), and extracted with CH_2Cl_2 (4 × 50 ml). The extracts are washed with H₂O (3 × 100 ml), dried (Na₂SO₄), and filtered through silica. Evaporation of the filtrate yields the thiourea [e.g. Ph, 92%, 4-tolyl, 86%; 4-MeOC₆H₄, 87%; 1-naphthyl, 59%; *o*-C₆H₄, 95%; cyclo-C₆H₁₁, 69%; $PhCH_2$, 72%; $-(CH_2)_4-$, 70%].

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4.4 SYNTHESIS OF SULPHONES AND SULPHOXIDES

As an alternative to the oxidation of sulphides and sulphoxides (see Chapter 10), sulphones can be prepared by the nucleophilic substitution reaction of the sulphinite anion on haloalkanes. In the absence of a phase-transfer catalyst, the reaction times are generally long and the yields are low, and undesirable *O*-alkylation of the sulphinite anion competes with *S*-alkylation. The stoichiometric reaction of the preformed tetra-*n*-butylammonium salt of 4-toluenesulphinic acid with haloalkanes produces 4-tolyl sulphones in high yield [1], but it has been demonstrated that equally good

TABLE 4.27
Selected examples of the liquid-phase synthesis of 4-tolyl sulphones

Haloalkane	Method	Reaction time	% yield
MeI	4.4.2.A	3 h	93
EtI	4.4.2.B	8 h/80–85°C	85
<i>iso</i> -PrBr	4.4.2.A	4 h/40°C	63
<i>iso</i> -PrI	4.4.2.B	6 h/80–85°C	89
<i>n</i> -C ₇ H ₁₅ Br	4.4.2.B	8 h/80–85°C	85
PhCH ₂ Cl	4.4.2.B	8 h/80–85°C	93
CH ₂ =CHCH ₂ Br	4.4.2.A	2.5 h	80
CH ₂ =C(Me)CH ₂ Cl	4.4.2.B	12 h/80–85°C	71
Me ₂ C=CHCH ₂ Br	4.4.2.B	12 h/80–85°C	87
MeOCH ₂ Cl	4.4.2.A	4 h/40°C	59
ClCH ₂ CN	4.4.2.A	3 h/30°C	85
4-ClC ₆ H ₄ CH ₂ Br	4.4.2.A	2 h	93
BrCH ₂ CO ₂ Et	4.4.2.A	2 h	80
MeCH(Br)CO ₂ Et	4.4.2.B	8 h/80–85°C	79
PhCOCH ₂ Br	4.4.2.A	2 h	81
ClCH ₂ COCH ₂ Cl	4.4.2.A	3 h	75 ^a
PhCH=CHCOCH ₂ Cl	4.4.2.A	2 h	85
CH ₂ Br ₂	4.4.2.A	4 h	89
CH ₂ I ₂	4.4.2.B	24 h/80–85°C	55
Br(CH ₂) ₂ Br	4.4.2.A	4 h/40°C	24 ^{b,c}
Br(CH ₂) ₃ Cl	4.4.2.A	4 h	93 ^d
2-Bromomethyloxirane	4.4.2.B		81 ^e
2-Chloromethyl-2-methyl-oxirane	4.4.2.B		95 ^f

^a (TosCH₂)₂CO using 2 equiv. of sulphinite; ClCH₂COCH₂Tos (75%) obtained, when 1 equiv. of sulphinite used.

^b Tos(CH₂)₂Tos + 45% TosCH=CH₂ using 1 equiv. of sulphinite. ^c 64% TosCH=CH₂ + 16% Tos(CH₂)₂Tos

obtained, when 2 equiv. of sulphinite used. ^d Tos(CH₂)₃Cl. ^e *trans*-TosCH=CHCH₂OH. ^f *E*-TosCH=C(Me)CH₂OH.

results are attainable under standard liquid:liquid two-phase conditions [2] (Table 4.27). However, the nucleophilicity of the sulphinite anion is such that, even in the presence of a phase-transfer catalyst, the liquid:liquid two-phase reaction is limited to the use of primary alkyl bromides and iodides and of secondary alkyl iodides. The corresponding reactions with bromomethyl and chloromethyl epoxides produces 3-(4-toluenesulphonyl) allyl alcohols [2] via a β -elimination reaction on the intermediate epoxy sulphones.

Using a solid:liquid two-phase system of the sodium arenesulphinite in 1,2-dimethoxyethane, or in the complete absence of a solvent, permits the use of less reactive haloalkanes [3, 4]. This is a particularly good method for the preparation of sulphones where the sulphinic acid salts are readily available and, in addition to the synthesis of the tolyl sulphones listed in Table 4.28, it has been used to prepare phenyl sulphones [3]. Phenyl sulphones have also been prepared in good yield using a polymer supported catalyst [5] (Table 4.29). As the system is not poisoned by iodide ions, reactive iodoalkanes can be used and there is the additional advantages in the ease of isolation of the product and the re-use of the catalyst.

TABLE 4.28

Selected examples of the solid:liquid two-phase synthesis of aryl sulphones

Haloalkane	Method	Reaction conditions	% yield
<i>4-Tolylsulphones</i>			
<i>iso</i> -PrBr	4.4.3.A	48 h/85°C	68
<i>n</i> -BuBr	4.4.3.A	4 h/85°C	94
PhCH ₂ Br	4.4.3.A	15 min/85°C	96
PhCH ₂ Br	4.4.3.B	2 h/85°C	85
2-CNC ₆ H ₄ CH ₂ Br	4.4.3.A	24 h/20°C	96
4-NO ₂ C ₆ H ₄ CH ₂ Br	4.4.3.B	2 h/85°C	93
CH ₂ =CHCH ₂ Br	4.4.3.A	20 min/85°C	90
PhCOCH ₂ Cl	4.4.3.A	30 min/85°C	96
ClCH ₂ CO ₂ Et	4.4.3.A	30 min/85°C	90
BrCH ₂ CN	4.4.3.B	2 h/60°C	85
<i>Phenyl sulphones</i>			
BrCH ₂ CN	4.4.3.B	2 h/60°C	91
ClCH ₂ CN	4.4.3.B	2 h/85°C	93
BrCH ₂ CO ₂ Me	4.4.3.B	4 h/60°C	95
BrCH ₂ CO ₂ Me	4.4.3.B	4 h/60°C	53
MeCH(Br)CO ₂ Me	4.4.3.B	4.5 h/60°C	88
ClCH ₂ CONH ₂	4.4.3.B	3 h/120°C	73
CH ₂ ClBr	4.4.3.B	24 h/85°C	47
MeCHClBr	4.4.3.B	24 h/85°C	35
PhCHClBr	4.4.3.B	24 h/60°C	95

4.4.1 Tetra-*n*-butylammonium 4-toluenesulphinite

TBA-Br (65 g, 0.2 mol) is added to 4-MeC₆H₄SO₂Na.2H₂O (85 g, 0.4 mol) in H₂O (125 ml) and the aqueous solution is extracted with CH₂Cl₂ (2 × 100 ml). The organic

TABLE 4.29
Polymer-supported synthesis of sulphones

Haloalkane	Reaction conditions	% yield
MeI	4.4,4/3 h	95
<i>iso</i> -PrI	4.4,4/3 h	94
<i>n</i> -C ₆ H ₁₃ Br	4.4,4/3 h	92
<i>n</i> -C ₈ H ₁₇ Br	4.4,4/3 h	92
<i>n</i> -C ₆ H ₁₃ CH(Me)Br	4.4,4/3 h	60 ^a
PhCH ₂ Cl	4.4,4/2 h	93
Me ₂ C=CHCH ₂ Br	4.4,4/1.5 h	95
ClCH ₂ CO ₂ Et	4.4,4/2 h	91
BrCH ₂ C(Me)=CHCO ₂ Et	4.4,4/1.5 h	92
BrCH ₂ CH=C(Me)CO ₂ Et	4.4,4/1.5 h	93
ClCH ₂ CN	4.4,4/2 h	95

^a Reaction conducted in refluxing toluene.

extracts are evaporated and final traces of H₂O are removed azeotropically with PhH from the quaternary ammonium sulphinite. ¹H NMR analysis of the crystalline product indicates it is a *ca.* 1 : 1 mixture of the *p*-toluene sulphinite and bromide salts.

4.4.2 Liquid phase synthesis of alkyl 4-tolyl sulphones

Method A: An equimolar amount of 4-MeC₆H₄SO₂-TBA in THF (50 ml) is added to the haloalkane (*ca.* 10 mmol) in THF (25 ml). The mixture is stirred at 20°C until GLC analysis indicates the complete consumption of the haloalkane (*ca.* 2–4 h) and it is then poured into saturated aqueous NH₄Cl (100 ml). The aqueous mixture is extracted with CHCl₃ (3 × 50 ml) and the extracts are washed with H₂O (2 × 25 ml), dried (MgSO₄), and evaporated to yield the sulphone, which can be recrystallized from EtOH.

Method B: 4-MeC₆H₄SO₂Na.2H₂O (17 g, 0.09 mol) is added to the alkylating agent (0.06 mol) and TBA-Br (15 g, 4.5 mmol) in a H₂O (20 ml):PhH (15 ml):Me₂CO (15 ml) system. The reaction mixture is stirred at 80–85°C until GLC analysis shows the complete disappearance of the alkylating agent and it is then poured into an Et₂O (50 ml):H₂O (50 ml) mixture. The organic phase is separated and the aqueous phase is extracted with Et₂O (2 × 25 ml). The combined organic solutions are dried (MgSO₄) and evaporated to yield the sulphone.

4.4.3 Solid:liquid two-phase preparation of 4-tolyl sulphones

Method A: The haloalkane (20 mmol) is added to a suspension of 4-MeC₆H₄SO₂Na.2H₂O (4.5 g, 21 mmol) and TBA-Br (0.32 g, 1.0 mmol) in MeO(CH₂)₂OMe (25 ml). The mixture is heated under reflux and then cooled to 0°C. Ice-water (100 ml) is added and the precipitated sulphone is collected, washed with H₂O and petroleum ether (b.p. 40–60°C).

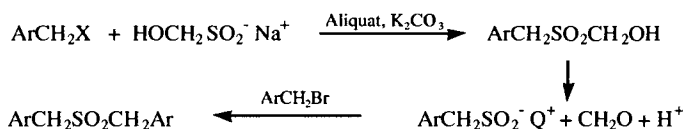
Method B: Aliquot (0.11 g, 0.2 mmol) is added to the haloalkane (10 mmol) and the sodium arenesulphinite (11 mmol). The mixture is vigorously shaken at room temperature for 5 min and then allowed to stand (Table 4.28). Et₂O or EtOAc (25 ml) is added and

the solution filtered through Florisil (2 g). The solvent is removed under reduced pressure and the product purified by recrystallization or by chromatography.

4.4.4 Polymer-supported synthesis of phenyl sulphones

Amberlyst A-26 resin (PhSO_2^- form) (11 g, *ca.* 40 mmol) and the haloalkane (5.8 g, 30 mmol) in PhH (30 ml) are stirred under reflux (Table 4.29). The resin is removed by filtration, washed with CH_2Cl_2 , and the combined organic solutions are evaporated under reduced pressure to yield the sulphone.

An alternative route to sulphones utilizes the reaction of the appropriate activated halide with sodium dithionite or sodium hydroxymethanesulphinite [6]. This procedure is limited to the preparation of symmetrical dialkyl sulphones and, although as a one-step reaction from the alkyl halide it is superior to the two-step oxidative route from the dialkyl sulphides, the overall yields tend to be moderately low (the best yield of 62% for dibenzyl sulphoxide using sodium dithionite is obtained after 20 hours at 120°C). The mechanism proposed for the reaction of sodium hydroxymethanesulphinite is shown in Scheme 4.20. The reaction is promoted by the addition of base and the best yield is obtained using Aliquat in the presence of potassium carbonate. It is noteworthy, however, that a comparable yield can be obtained in the absence of the catalyst. The reaction of phenacyl halides with sodium hydroxymethane sulphinite leads to reductive dehalogenation [7].



Scheme 4.20

4.4.5 Preparation of dibenzyl sulphones

Method A using sodium dithionite: PhCH_2Br (17.1 g, 0.1 mol) is added to $\text{Na}_2\text{S}_2\text{O}_4$ (10.44 g, 0.06 mol) and Aliquat (1.2 g, 3 mmol) and the mixture is shaken vigorously for 5 min and then heated to 120°C for 20 h. The dibenzyl sulphone is collected and is purified by chromatography on a short column of Florisil, using CH_2Cl_2 as the eluent, followed by recrystallization from EtOH: PhMe (1 : 1).

Method B using sodium hydroxymethanesulphinite: PhCH_2Br (17.1 g, 0.1 mol) is added to $\text{HOCH}_2\text{SO}_2\text{Na} \cdot 2\text{H}_2\text{O}$ (10.35 g, 0.06 mol), Aliquat (1.2 g, 3 mmol) and K_2CO_3 (10.35 g, 0.075 mol) and the mixture is heated with stirring for 20 h at 50°C . The dibenzyl sulphone is isolated and purified as described in 4.4.5.A.

Thione-S-oxides react regiospecifically with allyl and benzylsilanes in the presence of a stoichiometric amount of tetra-*n*-butylammonium fluoride to produce allyl and benzyl sulphoxides [8], *cf.* the analogous fluoride initiated reaction of thio-ketones and dithiocarboxylic esters with silanes [9, 10]. The yields of sulphoxides

tend to be higher from thione S-oxides derived from thioketones (55–75%) than they do for those S-oxides derived from dithiocarboxylic esters (30–60%).

4.4.6 Sulphoxides from thione-S-oxides

The thione S-oxide (0.21 mmol) and alkyl trimethylsilane (0.27 mmol) in dry DMF (2.6 ml) are added under N₂ to 'anhydrous' TBA-F (71 mg, 0.27 mmol) in dry DMF (2 ml) at room temperature.* The mixture is stirred at room temperature until the reaction is complete, as shown by TLC analysis. Aqueous NH₄Cl (sat. soln., 5 ml) is added and the mixture is extracted with Et₂O (3 × 15 ml). The dried (Na₂SO₄) extracts are evaporated to yield the sulphoxide. (*When allyltrimethylsilane is used, 4Å molecular sieves (0.3 g) are also added).

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4.5 S-ALKYLATION OF DIALKYL- AND DIARYLTHIOPHOSPHINATES

The S-alkyl thiophosphinates are obtained by the reaction of alkali metal salts of thiols with the phosphinyl chloride, but generally with unsatisfactory yields, and direct alkylation of thiophosphinates under basic conditions generally leads to a mixture of the S- and O-alkyl derivatives with the ratio of the two isomers depending, among other factors, on the choice of alkylating agent. In contrast, the solid:liquid two-phase alkylation of dialkyl- and diarylthiophosphinates, catalysed by tetra-*n*-butylammonium bromide, specifically forms the S-alkyl derivatives in good yield [1].

4.5.1 S-Alkylation of dialkyl- and diarylthiophosphinates

The dialkyl- or diarylthiophosphinate (0.1 mol), K₂CO₃ (13.8 g, 0.1 mol), TBA-Br (1.0 g, 3 mmol), and the haloalkane (0.12 mol) are stirred at 60°C (Table 4.30). When the reaction is complete, as shown by TLC analysis, the mixture is cooled to room temperature

TABLE 4.30
S-Alkylation of dialkyl- and diphenylthiophosphinates (R_2PSOH)

Thiophosphinate	Haloalkane	Reaction conditions	% yield
R = $n-C_5H_{11}$	n -BuBr	15 min/60°C	85
	<i>iso</i> -BuBr	5.5 h/60°C	40 ^a
	<i>sec</i> -BuBr	5.5 h/60°C	85 ^a
	<i>iso</i> -C ₅ H ₁₁ Br	2 h/60°C	54 ^a
$n-C_8H_{17}$	n -BuBr	15 min/80°C	91 ^a
<i>iso</i> -C ₅ H ₁₁	n -BuBr	30 min/60°C	97
	<i>iso</i> -BuBr	1 h/60°C	78
	<i>sec</i> -BuBr	8 h/60°C	36 ^a
	<i>iso</i> -C ₅ H ₁₁ Br	1 h/60°C	95
cyclo-C ₆ H ₁₁	n -BuBr	30 min/70°C	95
	<i>iso</i> -BuBr	2 h/70°C	91 ^a
	<i>sec</i> -BuBr	8 h/70°C	63 ^a
	<i>iso</i> -C ₅ H ₁₁ Br	15 min/70°C	98 ^a
Ph	n -BuBr	1 h/60°C	91
	<i>iso</i> -BuBr	2 h/60°C	38 ^b
	<i>sec</i> -BuBr	6 h/60°C	41 ^b
	<i>iso</i> -C ₅ H ₁₁ Br	1 h/70°C	98 ^a

^a in MeCN, ^b in PhH.

and Et₂O (50 ml) is added. The organic phase is separated, washed with H₂O (3 × 30 ml), dried (Na₂SO₄), and fractionally distilled to yield the S-alkyl thiophosphinate.

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4.6 S-N BOND FORMATION

The synthesis of aryloxysulphonyl azides, which can be used as precursors for sulphamates, is improved by the use of tetra-*n*-butylammonium azide under homogeneous conditions in place of an alkali metal azide [1]. A stoichiometric amount of the ammonium azide is used and no attempts appear to have been made to conduct the reaction under solid:liquid phase-transfer catalytic conditions.

4.6.1 Aryloxysulphonyl azides

TBA-N₃ (14.15 g, 50 mmol) in PhH (20 ml) is added over a period of *ca.* 10 min to a stirred solution of the aryloxysulphonyl chloride (50 mmol) in PhH (30 ml) at 20°C. The mixture is stirred for a further 10 min and the PhH is removed under reduced pressure. The residue is taken up in Et₂O (25 ml). The ethereal extracts are filtered and evaporated under reduced pressure to yield the azide (e.g. PhOSO₂N₃, 90%; 4-MeC₆H₄OSO₂N₃, 96%; 4-ClC₆H₄OSO₂N₃, 87%; 4-O₂NC₆H₄OSO₂N₃, 60%; PhC₆H₄OSO₂N₃, 95%).

N-(4-Toluenesulphonyl)sulphilimines, which are useful precursors in the synthesis of oxiranes and in alkylidene transfer reactions, have been prepared under solid:liquid phase-transfer catalytic conditions from Chloramine-T [2]. Comparable yields are obtained irrespective of whether the reaction is catalysed by Adogen or by benzyltriethylammonium chloride (Table 4.31). The procedure is an improvement on the liquid:liquid two-phase method [3].

TABLE 4.31
Synthesis of sulphanilimines

$$\text{R}^1\text{SR}^2 + \text{TosNClNa} \rightarrow \text{R}^1\text{SR}^2\text{NTos}$$

R^1SR^2	Reaction conditions		% yield
$\text{R}^1 = \text{Ph}$	$\text{R}^2 = \text{Me}$	4.6.2/2 h/Adogen	89 ^a
Ph	Me	4.6.2/3 h/TEBA-Cl	79
Ph	Ph	4.6.2/12 h/TEBA-Cl	73
<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	4.6.2/1 h/Adogen	87
<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	4.6.2/1 h/TEBA-Cl	82
Et	(CH ₂) ₂ OH	4.6.2/30 min/TEBA-Cl	56

^a 70% yield in the absence of a catalyst after 8 hours reaction period.

4.6.2 Synthesis of sulphanilimines using Chloramine T

Solid TosN(Cl)Na.3H₂O (15.5 g, 5.5 mmol) is added slowly to the thioether (0.05 mol) and either Adogen or TEBA-Cl (2.5 mmol) in CH₂Cl₂ (100 ml) at <10 °C and the mixture is stirred for 1–3 h until the reaction is complete, as shown by TLC analysis. The organic phase is washed with aqueous NaOH (5%, 200 ml) and H₂O (2 × 200 ml), dried (MgSO₄), and evaporated to yield the sulphanilimine.

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Formation of C–N Bonds and Related Reactions

5.1 ALKYLATION AND ACYLATION OF AMINES AND RELATED COMPOUNDS

The catalytic effect of quaternary ammonium salts in the basic liquid:liquid two-phase alkylation of amines [1–3] is somewhat unexpected in view of the low acidity of most amines ($pK_a > 30$). Aqueous sodium hydroxide is not a sufficiently strong base to deprotonate non-activated amines in aqueous solution and the hydroxide ion is not readily transferred into the organic phase to facilitate the homogeneous alkylation (see Chapter 1). Additionally, it is known that ion-pairs of quaternary ammonium cations with deprotonated amines are decomposed extremely rapidly by traces of water [4]. However, under solid:liquid two-phase conditions, the addition of a quaternary ammonium salt has been found to increase the rate of alkylation of non-activated amines by a factor of *ca.* 3–4 [5]. Similarly, the alkylation of aromatic amines is accelerated by the addition of the quaternary ammonium salt; the reaction is accelerated even in the absence of an inorganic base, although under such conditions the amine is deactivated by the formation of the hydrohalide salt, and the rate of the reaction gradually decreases. Hence, the addition of even a weak base, such as

TABLE 5.1
Influence of base upon *N*-alkylation of amines^a

Base	Catalyst	mmol of base	% yield	
			With catalyst	Without catalyst
Solid KOH	TBA-Cl	40	44	13
50% aq. NaOH	TBA-Cl	100	70	12
50% aq. NaOH	TBA-Cl	11	68	11
10% aq. NaOH	TBA-Cl	20	44	12
Solid K ₂ CO ₃	TBA-Cl	20	63	18
Solid K ₂ CO ₃	TBA-Cl	20	62	9
Solid K ₂ CO ₃	TBA-Br	20	60	9

^a 10 mmol PhNHMe, 10 mmol *n*-C₆H₁₃Br, 0.25 mmol catalyst in PhMe (10 ml) at 100 °C for 15.5 h.

potassium hydrogen carbonate, increases the rate of alkylation markedly (Table 5.1). It is notable that, although potassium hydroxide is a stronger base, its addition in the solid form frequently leads to tars and lowers the overall yield of alkylated product whereas, in contrast, aqueous sodium hydroxide has been effectively employed. Although potassium carbonate has been used successfully for the preparation of alkylated amines, e.g. α -(*N*-perfluoroalkylamino)acetic acids [6], it may lead to the formation of carbamates under solid:liquid conditions [7].

It is noteworthy that benzyltriethylammonium chloride is a slightly better catalyst than the more lipophilic Aliquat or tetra-*n*-butylammonium salts (Table 5.2). These observations obviously point to a mechanism in which deprotonation of the amine is not a key catalysed step. As an extension of the known ability of quaternary ammonium halides to form complex ion-pairs with halogen acids in dichloromethane [8], it has been proposed that a hydrogen-bonded ion-pair is formed between the catalyst and the amine of the type $[Q^+X^--H-NR_2]$ [5]. Subsequent alkylation of this ion-pair, followed by release of the cationic alkylated species, $ArRR'_2NH^+$, from the ion-pair and its deprotonation at the phase boundary is compatible with all of the observed facts.

It has been reported that the ease of *N*-alkylation of aromatic amines is enhanced by ultrasonics [9], and, predictably, the presence of mesomeric electron-withdrawing substituents at positions *ortho* or *para* to the amino function aids the *N*-alkylation of the aromatic amines [e.g. 10], see also, for example, the phase-transfer catalysed glycosidation of 2-cyanoaniline [11]. Generally, the direct *N*-monoalkylation of aminoarenes is not particularly satisfactory, but an alternative protocol [12] in which the *N*-acyl derivatives are alkylated and then hydrolysed leads to enhanced yields (>90%) (see Section 5.2). In a similar manner, a 'one pot' synthesis converts 2-

TABLE 5.2
Effect of catalyst of *N*-alkylation of aromatic amines^a

Amine	Catalyst	% conversion ^b	% yield ^c	
			<i>N</i> -alkylation	<i>N,N</i> -dialkylation
PhNH ₂	None	32	24	4
	Aliquat	66	44	11
	TEBA-Cl	95	51	22
	TBA-HSO ₄	87	45	16
	TBA-Br	89	49	20
	THA-Br	72	44	14
4-MeC ₆ H ₄ NH ₂	None	16	12	2
	TBA-HSO ₄	77	47	15
4-MeOC ₆ H ₄ NH ₂	None	25	19	0
	TBA-HSO ₄	76	46	14
2-O ₂ NC ₆ H ₄ NH ₂	None	0	0	0
	TBA-HSO ₄	42	42	0

^a 40 mmol amine, 40 mmol EtBr, 1 mmol catalyst, and 40 mmol crushed NaOH at 40°C for 2 h. ^b Based on consumed EtBr. ^c GLC analysis.

nitroanilines into their *N*-alkyl derivatives via the trifluoroacetanilides. This procedure provides an extremely convenient route to *N*-alkyl-1,2-diaminobenzenes [13]. Caution has to be exercised in the *N*-alkylation of 2-amino-2'-halobenzophenones under solid:liquid two-phase conditions for, although yields are generally high (>90%) [14], the yield of the product obtained from the 2'-fluoro derivative is lowered by the intramolecular S_NAr reaction yielding the acridone.

Care must be taken in the choice of organic solvent. Chloroform should never be used under the basic conditions due to the risk of the formation of isocyanides (see Chapter 7) and the use of carbon disulphide can lead to formation of dithiocarbamates, e.g. dimethyl *N*-(ethoxycarbonylmethyl)iminodithiocarbonate is formed (35–39%), as the major product in high purity, in the liquid:liquid two-phase methylation of ethyl glycinate in carbon disulphide [15]. The product is useful as an intermediate in the synthesis of thiazoles [15] and dihydrooxazoles [16].

5.1.1 Mono-*N*-alkylation of anilines under solid:liquid two-phase conditions

Powdered NaOH (160 g) is added to the aniline (1 mol) and TBA-Br (3.22 g 10 mmol) in THF (2000 ml) at room temperature. The mixture is stirred for *ca.* 5 min and the alkylating agent (3 mol) is then added and the mixture is stirred at 60°C for 1 h. Volatile material is removed under reduced pressure and the residue is taken up in the minimum amount of EtOAc. The organic solution is washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the *N*-alkylated derivative.

5.1.2 'One-pot' preparation of *N*-alkyl-2-nitroanilines via their trifluoroacetyl derivatives

(CF₃CO)₂O (4.29 g, 20 mmol) is added dropwise with stirring to the 2-nitroaniline (10 mmol) in CH₂Cl₂ (20 ml) at 0°C, and then NaHCO₃ (sat. soln, 10 ml) is added dropwise. The mixture is allowed to come to room temperature and is stirred for 30 min. The organic phase is separated, and the aqueous phase is extracted with CH₂Cl₂ (2 × 25 ml). The dried (MgSO₄) organic solutions are evaporated to give the crude trifluoroacetanilide (10 mmol), which is then added to TEBA-Cl (2.45 g, 10 mmol) and the alkylating agent (12.5 mmol) in PhMe (20 ml). Aqueous NaOH (50%, 10 ml) is added and mixture stirred until TLC analysis indicates that the reaction is complete. The reaction is quenched with aqueous NH₄Cl (sat. soln.) and the organic phase is separated. The aqueous phase is extracted with EtOAc (3 × 25 ml) and the combined organic solutions are dried (MgSO₄) and evaporated to yield the *N*-alkyl-2-nitroaniline.

Reaction of 2-aminopyrroles with equimolar amounts of dimethyl sulphate under phase-transfer catalysed basic conditions produces the 2-amino-1-methylpyrrole in good yield [17]. When two equivalents of the alkylating agent are used, a mixture of the mono- and dimethylamino-1-methylpyrroles and 2-amino-1-methylpyrroles is obtained.

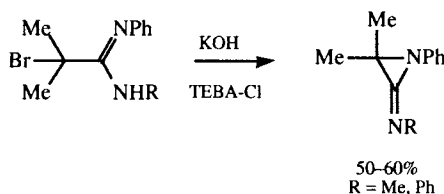
Phase-transfer catalysis has been used to aid the synthesis of sterically hindered α -aminocarboxamides [18] (Table 5.3). No intramolecular cyclization of the sterically

TABLE 5.3
Synthesis of α -aminocarboxamides

$\text{BrCR}^1(\text{R}^2)\text{CONH}_2$		$\text{R}^3\text{R}^4\text{NH}$		Reaction time	% yield
$\text{R}^1 = \text{Me}$	$\text{R}^2 = \text{Me}$	$\text{R}^3 = \text{Et}$	$\text{R}^4 = \text{Et}$	6 h	73
Me	PhCH_2	Et	Et	4 h	74
Me	PhCH_2	$-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$		4 h	80
Et	PhCH_2	Et	Et	8 h	80
Me	PhCH_2	$\text{C}_{10}\text{H}_{15}^a$	H	10 h	68

^a 1-adamantyl.

hindered α -bromocarboxamides occurs under the basic conditions, but a similar phase-transfer catalysed reaction of α -bromoamidines yields iminoaziridines (Scheme 5.1) [19].



Scheme 5.1

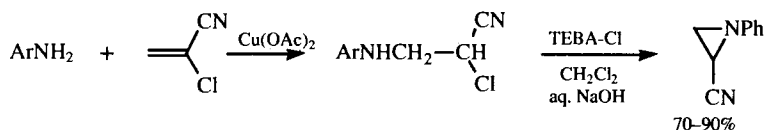
5.1.3 Synthesis of α -aminocarboxamides

The α -bromoamide (3 mmol), the amine (or its salt) (3.5 mmol) and TBA-Br (97 mg, 0.3 mmol) are added to a stirred two-phase system of aqueous NaOH (50%, 10 ml) and CH_2Cl_2 (12 ml). Stirring is continued for a further 4–10 h (see Table 5.3). H_2O (10 ml) is then added and the organic phase is separated and washed with H_2O (3×50 ml) and HCl (1M, 3×30 ml). The combined aqueous phases are neutralized with NaHCO_3 and extracted with CH_2Cl_2 (3×50 ml). The dried (MgSO_4) organic extracts are evaporated to yield the aminocarboxamide, which is purified by chromatography from silica.

5.1.4 Synthesis of iminoaziridines

Powdered KOH (5 g, 0.89 mol) and TEBA-Cl (0.84 g, 3.7 mmol) are added to the α -bromoamidine (24.6 mmol) in Et_2O (100 ml) at -60°C . The mixture is stirred at -60°C for 2 h, filtered, and evaporated at 0°C under reduced pressure to yield the aziridine.

A similar intramolecular cyclization of 3-arylamino-2-chloropropanonitriles under basic conditions to yield 1-aryl-2-cyanoaziridines (Scheme 5.2) also proceeds more smoothly when benzyltriethylammonium chloride is added to the reaction mixture [20]. The procedure is not suitable, however, for the preparation of *N*-alkyl analogues.

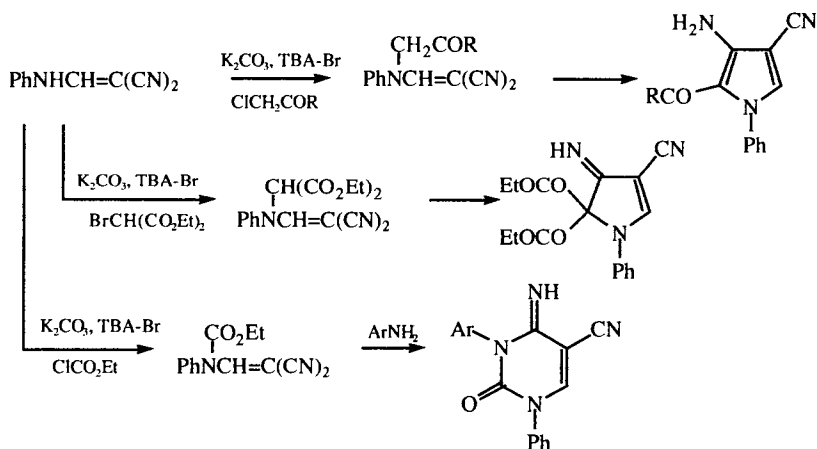


Scheme 5.2

5.1.5 Synthesis of 1-aryl-2-cyanoaziridines

TEBA-Cl (0.5 g, 2.2 mmol) in aqueous NaOH (50%, 10 ml) is added with stirring to the 3-aryl-2-chloropropanonitrile (0.01 mol) in CH_2Cl_2 (20 ml) at room temperature. Stirring is continued until TLC analysis indicates the completion of the reaction (*ca.* 1–3 h). H_2O (50 ml) and CH_2Cl_2 (20 ml) is then added and the organic phase is separated, washed with H_2O (2×100 ml), dried (Na_2SO_4), and evaporated under reduced pressure to give the aziridine, which is purified by chromatography from silica.

The products from the *N*-alkylation of (anilinomethylene)malonodinitriles with α -haloacetic esters and α -haloketones spontaneously cyclize to produce pyrroles (Scheme 5.3) [21]. When the *N*-acylated product of the reaction of the dinitrile with ethyl chloroformate is treated with an arylamine, 5-cyanopyrimidones are obtained [21].



Scheme 5.3

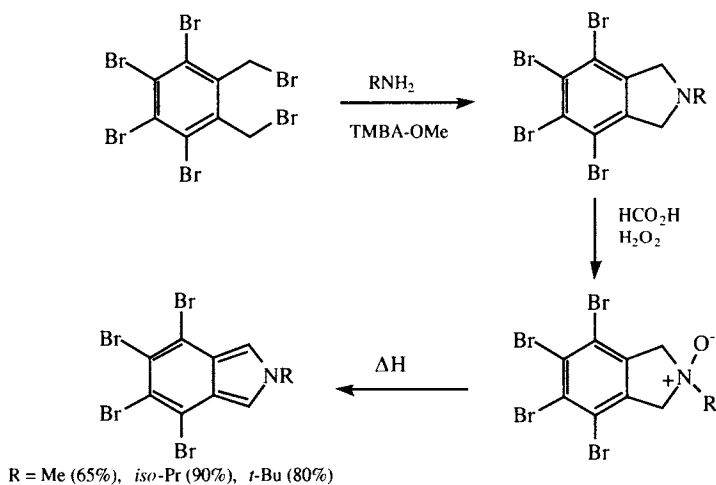
5.1.6 Heterocycles from (anilinomethylene)malonodinitriles

Pyrroles: The alkylating agent, ClCH_2COR (3 mmol), and TBA-Br (20 mg, 0.06 mmol) is added to $\text{PhNHCH}=\text{C}(\text{CN})_2$ (0.5 g, 3 mmol) and K_2CO_3 (3 g) in dioxan (40 ml) and the mixture is stirred at 95°C until the reaction is shown to be complete by TLC analysis

(3–8 h). The filtered organic solution is washed well with H_2O , dried (MgSO_4), and evaporated to yield the pyrrole [$\text{R} = \text{OEt}$ (85%); Ph (88%)]. The corresponding reaction with $\text{BrCH}(\text{CO}_2\text{Et})_2$ yields the 2,3-dihydropyrrole (70%).

Pyrimidones: ClCO_2Et (0.33 g, 3 mmol) and TBA-Br (20 mg, 0.06 mmol) is added to $\text{PhNHCH}=\text{C}(\text{CN})_2$ (0.5 g, 3 mmol) and K_2CO_3 (3 g) in dioxan (40 ml) and the mixture is stirred at 75°C for 7.5 h. The filtered organic solution is washed well with H_2O , dried (MgSO_4), and evaporated to yield the *N*-ethoxycarbonyl derivative (75%), which upon reflux with an arylamine for *ca.* 4 h yields the pyrimidone (60–70%).

In the conversion of 3,4,5,6-tetrabromo-1,2-bis(bromomethyl)benzene into the tetrabromoisindole (Scheme 5.4), the bisalkylation of the primary amine in the first step of the reaction is promoted by the addition of benzyltrimethylammonium methoxide [22]. 2-Chloromethylpyridine reacts with a series of α,ω -diaminoalkanes, as well as 1,2-diaminobenzene, to produce *N,N'*-dialkylated and *N,N,N,N'*-tetraalkylated products [23].



Scheme 5.4

The strongly acidic character of cyanamide, compared with simple amines, results in its facile dialkylation by a range of reagents [24]. Reaction with α,ω -dihalogeno compounds leads to cyclic products (Table 5.4).

5.1.7 *N*-Alkylation of cyanamide

The addition of NH_2CN (2.1 g, 0.05 mol) to aqueous NaOH (50%, 20 ml for chloroalkanes, 33 ml for bromoalkanes, and 50 ml for α,ω -dibromoalkanes) is exothermic. The mixture is stirred during the addition and cooled to room temperature. Aliquat (0.3 g, 0.75 mmol) and an excess of the haloalkane (0.125 mol) is added [PhH

TABLE 5.4
N,N-Dialkylation of cyanamides

Alkylating agent	% yield	Alkylating agent	% yield
MeBr	32 ^a	MeOCH ₂ Cl	71 ^a
EtBr	75	<i>n</i> -BuOCH ₂ Cl	72 ^a
<i>iso</i> -PrBr	54	Br(CH ₂) ₄ Br	85
<i>n</i> -BuBr	80	Br(CH ₂) ₅ Br	75
PhCH ₂ Cl	96	Br(CH ₂) ₆ Br	25
CH ₂ =CHCH ₂ Cl	91	1,2-(BrCH ₂) ₂ C ₆ H ₄	50

^a reaction conducted at 0–5°C.

(19 ml) is also added for the reaction with the α,ω -dibromoalkanes]. The two-phase system is extracted with PhH (3 \times 25 ml) and the organic extracts are washed with brine (2 \times 20 ml), dried (MgSO₄), and evaporated to yield the alkylated product.

Alkylation of the more acidic hydrazo [25] and triazene [26] systems proceeds readily under liquid:liquid two-phase conditions, using tetra-*n*-butylammonium hydroxide and benzyltriethylammonium chloride, respectively, as the catalysts (Tables 5.5 and 5.6).

As indicated in Table 5.5, the addition of an inorganic salt appears to improve the yields of the *N*-alkylated hydrazobenzenes by a common ion effect. In the absence of the inorganic salt, the best yields in the shortest reaction times are attained when chlorobenzene is used as the organic phase. Stoichiometric amounts of the catalyst are used in this reaction and it is conceivable that either the solid:liquid or the liquid:liquid two-phase conditions, with a catalytic amount of the ammonium salt, as used in the *N*-alkylation of the triazenes, may be a more effective process.

TABLE 5.5
N-Alkylation of hydrazobenzene

Haloalkane	% yield ^a		
	in CH ₂ Cl ₂	in CH ₃ CHCl ₂	in PhCl
MeI	39 ^b (2 h)	34 (70 min)	40 (34 min)
EtBr	7 ^c (5 h)		
EtI	40 ^d (24 h)	20 (4 h)	28 (40 min)
<i>n</i> -PrBr	13 ^e (96 h)		
<i>iso</i> -PrI	13 ^e (24 h)		
PhCH ₂ Br	79 ^c (1 h)		
CH ₂ =CHCH ₂ Br	59 ^f (70 min)	42 (42 min)	49 (9 min)

^a Reaction times given in parentheses. ^b 79% after 21 h, when 1 mol equivalent of NaI added.

^c 1 mol equivalent of KBr added. ^d 42% after 24 h, when 1 mol equivalent of NaI added. ^e 1 mol equivalent of NaI added. ^f 79% after 22 h, when 1 mol equivalent of KBr added.

TABLE 5.6
Selected examples of the *N*-alkylation of 1,3-diaryltriazenes

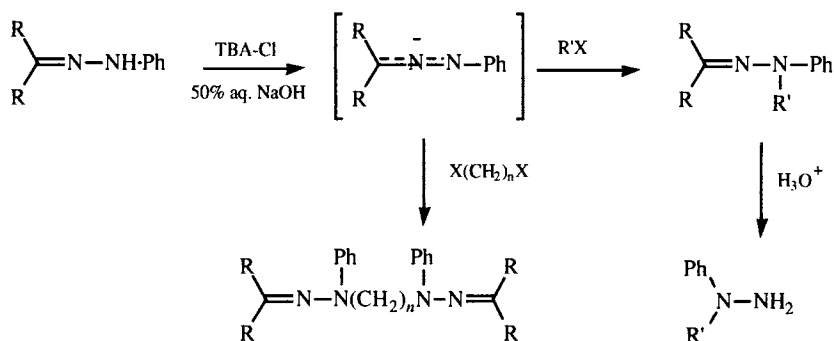
ArN=NNHAr	Haloalkane	% yield
Ar = 4-MeOC ₆ H ₄ 4-MeC ₆ H ₄ Ph 4-BrC ₆ H ₄ 4-ClC ₆ H ₄ 4-FC ₆ H ₄ 4-MeCOC ₆ H ₄ 4-EtOCOC ₆ H ₄	EtBr	80
	MeI	80
	CH ₂ =CHCH ₂ Br	90
	PhCH ₂ Cl	90
	CH ₂ =CHCH ₂ Br	80
	MeI	80
	EtBr	75
	<i>n</i> -BuBr	85
	PhCH ₂ Cl	80
	CH ₂ =CHCH ₂ Br	85
	CH ₂ =CHCH ₂ Br	85
	MeI	90
	EtBr	55
	<i>n</i> -BuBr	70
	PhCH ₂ Cl	75
	CH ₂ =CHCH ₂ Br	90
	MeI	75
	EtBr	70
	<i>n</i> -BuBr	70
	PhCH ₂ Cl	85
	CH ₂ =CHCH ₂ Br	80

5.1.8 *N*-Alkylation of 1,3-diaryltriazenes

Method A: The reactive haloalkane (10 mmol) is added to a stirred solution of the triazene (5 mmol) and TEBA-Cl (0.11 g, 0.5 mmol) in aqueous NaOH (50%, 20 ml) and PhH (40 ml) at 50–60°C. When TLC analysis shows the reaction to be complete (a colour change in the organic phase from red to yellow–orange is noted at the end of the reaction. *ca.* 10–15 min), the PhH phase is separated, washed with H₂O (2 × 50 ml), and dried (MgSO₄). Evaporation under reduced pressure yields the alkylated product.

Method B (for weakly reactive alkyl halides): The alkyl halide (10 mmol) is added to the triazene (5 mmol), TEBA-Cl (0.11 g, 0.5 mmol), and an excess of crushed NaOH (0.5 g) in xylene at 100–120°C. The mixture is stirred for 1 h, and H₂O is then added, and the product is isolated by the procedure outlined in 5.1.8.A.

The facile phase-transfer catalysed *N*-alkylation of phenylhydrazones provides an effective route to *N*-alkyl-*N*-phenylhydrazines, as shown in Scheme 5.5 [27]. Deprotonation of both the hydrazones and the triazenes leads to resonance stabilized anions. It is therefore highly probable that the alkylation occurs on the initially formed anions, instead of the neutral species, as indicated by the red colour imparted to the organic phase in the reactions of the triazenes, which results from the formation of the ion-pair [Q⁺ ArN=N-NAr⁻].



Scheme 5.5

5.1.9 *N*-Alkylation of phenylhydrazones

The phenylhydrazone (0.02 mol) and the haloalkane (0.03 mol) are added with stirring to TBA-Cl (0.3 g, 1.1 mmol) in aqueous NaOH (50%, 20 ml). The mixture is stirred for 0.5–3 h at 30–60°C (Table 5.7) and then poured into H_2O (100 ml). The alkylated product generally precipitates from the mixture and can be recrystallized. Liquid products are extracted from the mixture with $CHCl_3$ (3×25 ml). The extracts are washed with H_2O (4×25 ml), dried ($MgSO_4$), and evaporated under reduced pressure.

Although there are few reports of catalysed acylation or sulphonylation reactions of simple amines in which the amides are isolated, the synthesis of carboxamides and

TABLE 5.7
Selected examples of the *N*-alkylation of phenylhydrazones

$PhNHN=CR^1R^2$		Haloalkane	Reaction conditions	% yield
$R^1 = Ph$	$R^2 = H$	MeI	3 h/50°C ^a	92
		<i>n</i> -PrBr	1 h/60°C	70
		$PhCH_2Cl$	0.5 h/60°C	98
		$BrCH_2CO_2i-Bu$	0.5 h/ 3–7°C ^b	59
		$CH_2=CHCH_2Br$	2 h/30°C	78
		$CH_2=CHCH_2Cl$	0.5 h/40°C	85
		$CH=CCH_2Cl$	0.5 h/40°C	85
		$Br(CH_2)_nBr$	0.5 h/45°C	70 ($n = 1$)
				75 ($n = 2$)
4- $NO_2C_6H_4$	H	<i>n</i> -PrBr	2 h/50°C	76
		$PhCH_2Cl$	0.5 h/60°C	91
Me	Me	$PhCH_2Cl$	1.5 h/50°C	52
Ph	Ph	<i>n</i> -PrBr	2 h/50°C	50
		$PhCH_2Cl$	1 h/50°C	72
		<i>n</i> -PrBr ^a	1 h/40°C	43
		$PhCH_2Cl$	0.5 h/50°C	56

^a 40 mmol of alkylating agent used. ^b 20 mmol of alkylating agent used.

peptides from carboxylic acids, using amines and phosphonate esters [e.g. 28] or preformed phosphoramides [e.g. 29], is aided by the addition of quaternary ammonium salts [28–31]. Intramolecular acylation of β -aminocarboxylic acids produces β -lactams in high yield [31]. As an alternative to direct acylation of amines with acid chlorides, amides have been obtained under very mild conditions using acid fluorides and silylamines in the presence of tetra-*n*-butylammonium fluoride [32]. The procedure is extremely useful, when the acid chlorides are unstable as, for example, 2-pyrrolylcarbonyl chloride.

5.1.10 Amides from silylamines

The acid fluoride (3 mmol), obtained from the carboxylic acid and cyanuric fluoride, and TBA-F (5 mg, 0.02 mmol) are added to the silylamine (3 mmol) in MeCN (5 ml) under N_2 and the solution is stirred for 6 h at room temperature. The solvent is removed under reduced pressure and the residue is taken up in CH_2Cl_2 . The organic solution is washed with aqueous $NaHCO_3$ (5%, 2×10 ml), aqueous HCl (4M, 2×10 ml) and H_2O (20 ml), dried (Na_2SO_4), and evaporated to yield the amide (>75%).

5.1.11 Conversion of carboxylic acids into carboxamides

The amine (0.54 mmol) in CH_2Cl_2 (2 ml) and K_2CO_3 (0.14 g, 1.4 mmol) is added with stirring to the acid (0.45 mmol), KOH (30 mg, 0.5 mmol), and TBA- HSO_4 (15 mg, 0.045 mmol) in H_2O (3 ml) and CH_2Cl_2 (2 ml) and the mixture is stirred for 30 min. Bis(2-nitrophenyl)phenylphosphonate (0.22 g, 0.54 mmol) in CH_2Cl_2 (2 ml) is added and the mixture is stirred for a further 4 h. EtOAc (10 ml) and H_2O (10 ml) are added and the organic phase is separated, washed with brine (2×15 ml), dried (Na_2SO_4), and evaporated to yield the amide.

5.1.12 β -Lactams from β -aminocarboxylic acids

CH_3SO_2Cl (0.23 g, 2 mmol) in $CHCl_3$ (5 ml) is added to the β -amino acid (1 mmol), $KHCO_3$ (0.4 g, 4 mmol) and TBA- HSO_4 (51 mg, 0.15 mmol) and the mixture is stirred for 24 h at room temperature. Et_2O (10 ml) and H_2O (10 ml) are added and the organic phase is separated, washed well with brine, dried (Na_2SO_4), and evaporated to yield the β -lactam (1,3-disubstituted azetidones: $PhCH_2$, Me, 87%; $PhCH_2$, *n*-Pr, 84%; $PhCH_2$, Ph, 82%; $PhCH_2$, CO_2Me , 60%; *n*- C_6H_{13} , Me, 80%; cyclo- C_6H_{13} , Me, 81%).

The direct formation of *N*-substituted phthalimides from phthalic anhydride and alkyl azides, via the intermediate $RN=PPh_3$ compound, is catalysed by the presence of tetra-*n*-butylammonium cyanide [34].

1,2-Disubstituted hydrazines and semicarbazones react with α -haloacyl halides under two-phase catalytic conditions to produce 1,2-diazetidin-3-ones (20–85%) [35], whereas β -haloacyl halides react with hydrazines to form pyrazolin-3-ones (ca. 30%).

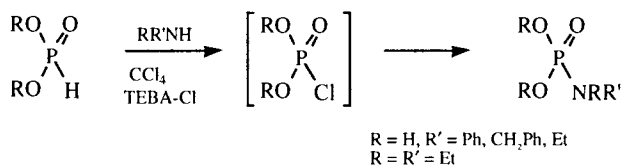
A two-phase modification of the traditional Atherton–Todd phosphorylation reaction (Table 5.8) is aided by the addition of benzyltriethylammonium chloride [36, 37]

TABLE 5.8
Phosphorylation of primary and secondary amines with (EtO)₂PHO

R ¹ R ² NH	Method	% yield of R ¹ R ² NPO(OEt) ₂
R ¹ = Ph R ² = H	5.1.13.A	100 ^a
4-ClC ₆ H ₄ H	5.1.13.A	76
Et H	5.1.13.B	83 ^b
<i>n</i> -Bu H	5.1.13.D	100
PhCH ₂ H	5.1.13.A	85
cyclo-C ₆ H ₁₁ H	5.1.13.A	89
	5.1.13.B	100
(CH ₂) ₂ OH H	5.1.13.A	100
Et Et	5.1.13.A	86
(CH ₂) ₃ OH H	5.1.13.A	100
(CH ₂) ₂ OH (CH ₂) ₂ OH	5.1.13.A	100
-(CH ₂) ₂ O(CH ₂) ₂ -	5.1.13.A	100

^a 87% by **5.1.13.B**, ^b 81% by **5.1.13.C** using the amine salt.

(Scheme 5.6). The reaction can be conducted under basic liquid:liquid conditions but, in order to minimize hydrolysis of the phosphite and to prevent carbene formation, a milder solid (KHCO₃):liquid system with tetra-*n*-butylammonium bromide is preferred. Under these conditions, yields are almost quantitative [38]. Tetra-bromomethane is generally recommended, in preference to tetrachloromethane, for reactions with weakly basic aryl-amines.



Scheme 5.6

The ease with which the phosphorylation can be carried out and the simple reversal to the amine upon treatment with gaseous hydrogen chloride in tetrahydrofuran at room temperature provides a convenient procedure for the protection of amines.

The analogous phosphorylation of hydrazines [37] proceeds smoothly to produce the monophosphorylated derivatives in high yield (Table 5.9).

TABLE 5.9
Phosphorylation of hydrazine with (RO)₂PHO

(RO) ₂ PHO	Method	% yield of (RO) ₂ PONHNH ₂
R = Et	5.1.13.E	84
<i>n</i> -Pr	5.1.13.E	90
<i>iso</i> -Pr	5.1.13.E	74
<i>n</i> -Bu	5.1.13.E	98
<i>t</i> -Bu	5.1.13.E	41

5.1.13 Atherton–Todd phosphorylation of amino compounds

Method A: The dialkyl phosphite (0.125 mol) and the amine (0.1 mol) in CH_2Cl_2 (30 ml) are added dropwise to a mixture of CCl_4 (30 ml), CH_2Cl_2 (30 ml), TEBA-Cl (1.0 g, 4.4 mmol), and aqueous NaOH (20%, 40 ml) with stirring at such a rate to contain the strongly exothermic reaction below 5°C (external cooling with an ice–salt bath will be necessary). When the addition is complete, the mixture is stirred for a further 1 h at 0 – 5°C , and then at room temperature for 1 h. CH_2Cl_2 (25 ml) is added and the organic phase is separated, washed with HCl (5%, 50 ml) and H_2O (2×50 ml), dried (MgSO_4), and evaporated to yield the phosphoramidate.

Method B: The procedure is analogous to 5.1.13.A, except that CBr_4 (16.6 g, 0.05 mol) replaces CCl_4 and the reaction is conducted at room temperature. The phosphoramidate is isolated by the procedure described in 5.1.13.A.

Method C: Aqueous NaOH (30%, 40 ml) is added dropwise with stirring to the dialkyl phosphite (0.125 mol), the amine (0.1 mol), CCl_4 (40 ml), CH_2Cl_2 (40 ml) and TEBA-Cl (1.0 g, 4.4 mmol) at 0 – 5°C . The two-phase system is stirred for 2 h at room temperature and then diluted with CH_2Cl_2 (50 ml) and worked up as described in 5.1.13.A.

Method D: $(\text{EtO})_2\text{PHO}$ (6.9 g, 50 mmol) in CCl_4 (10 ml or 30 ml when an amine salt is used) is added dropwise with stirring to the amine or amine salt (50 mmol), KHCO_3 (10 g), and TBA-Br (0.8 g, 2.5 mmol) in CH_2Cl_2 (40 ml) at 10 – 15°C . The reaction is exothermic and requires external cooling. The mixture is stirred at 15 – 20°C for 2 h (4 h for the amine salt) and then allowed to stand at room temperature for 12 h. The mixture is filtered and the solid washed with CH_2Cl_2 (2×25 ml). The combined organic solutions are evaporated to yield the phosphorylated amine.

Method E: Aqueous NH_2NH_2 (80%, 12.5 g, 0.2 mol) is added dropwise with stirring to powdered K_2CO_3 (41.4 g, 0.3 mol) and TEBA-Cl (0.4 g, 1.75 mmol) in CCl_4 (120 ml) and CH_2Cl_2 (200 ml) at 20 – 25°C . The mixture is stirred for 15 min at room temperature and the dialkyl phosphite (0.2 mol) in CH_2Cl_2 (40 ml) is then added dropwise at 20 – 30°C . Stirring is continued for *ca.* 4 h at room temperature and the solids are then removed by filtration and washed with CH_2Cl_2 . The combined organic solutions are evaporated under reduced pressure and the residue is maintained at 100 – 110°C under 0.5 mm Hg in order to remove volatile impurities and to produce analytically pure samples of the phosphorohydrazines.

Aliquat is an efficient catalyst for the acetoacetylation of amines by diketene. The initially formed amides react with an excess of the diketene to form, after cyclization of the secondary product, 1-substituted 3-acetyl-4-hydroxy-6-methylpyrid-2-ones [39]. Amides react under similar conditions with diketene to form *N*-acyl acetoacetamides, which react further with a second molecule of diketene to yield, after cleavage of the *N*-acyl group, 3-acetyl-4-hydroxy-6-methylpyrid-2-one [39].

5.1.14 Acetoacetylation of amines and amides

The amine or amide (50 mmol) and Aliquat (0.81 g, 2 mmol) in PhMe (20 ml) are stirred at 70 – 90°C and diketene (6.73 g, 80 mmol) is added dropwise. The mixture is stirred for 8–10 h and then cooled, filtered, and evaporated. The residue is extracted with Et_2O (3×25 ml) and the extracts are evaporated to yield the acetoacetylated product

MeCOCH₂CONHR (e.g. R=COPh, 94%; COCH₂Ph, 92%, COCH₂CH=CH₂, 68%; COEt, 70%). Further reaction of the product with diketene (80 mmol), or if 0.24 mol of diketene is initially added, 1-substituted 3-acetyl-4-hydroxy-6-methylpyrid-2-one is formed (e.g. 1-substituent: Ph, ~100%; COPh, 89%; COCH₂Ph, 87%, COCH₂CH=CH₂, 59%; COEt, 83%).

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5.2 ALKYLATION OF AMIDES AND RELATED COMPOUNDS

The acidity of amides ($pK_a \sim 23$) is such that it is reasonable to postulate that, in contrast with the analogous reactions of the amines, the phase-transfer catalysed *N*-alkylation proceeds by way of the initial generation of the amidic anion under basic conditions. It has been demonstrated that the preformed sodium salt of benzamide can be solubilized in toluene upon the addition of Aliquat [1] and further evidence [2] has been provided for the postulated deprotonation under the two-phase conditions in which it is assumed that the deprotonation occurs by an interfacial mechanism (see Chapter 1).

Mono-*N*-alkylation of the amides occurs under relatively mild liquid:liquid two-phase conditions (Table 5.10), using concentrated aqueous sodium or potassium hydroxide. Under solid:liquid conditions with sodium hydroxide–potassium carbonate or potassium hydroxide, or by using ‘super-saturated’ aqueous potassium or sodium hydroxide, it is possible to control the reaction to obtain either the mono- or dialkylated derivatives [2–4]. Solid:liquid two-phase conditions also provide the most effective route to mono-*N*-alkylation of weakly acidic aliphatic amides, but it has been suggested that the procedure is not sufficiently selective for the mono-alkylation of the more acidic amides [4].

5.2.1 Monoalkylation of amides

Method A: The haloalkane (0.06 mol) in PhH (10 ml) is added dropwise over a period of *ca.* 1.5 h to the amide (0.05 mol) and TBA- HSO_4 (1.7 g, 5 mmol) in a stirred two-phase system of aqueous NaOH (50%, 50 ml) and PhH (50 ml) under reflux. Stirring is continued for a further 2.5 h under reflux and the mixture is then cooled to room temperature and H_2O (30 ml) is added. The organic phase is separated, washed with H_2O until neutral, dried (MgSO_4), and evaporated under reduced pressure to yield the alkylated amide.

TABLE 5.10
Selected examples of the *N*-alkylation of carboxamides

Haloalkane	Method	% yield
<i>N</i> -Alkylation of benzamide		
EtBr	5.2.1.A	73
<i>n</i> -PrBr	5.2.1.A	80
<i>iso</i> -PrBr	5.2.1.A	32
<i>n</i> -BuBr	5.2.1.A	79 ^a
<i>iso</i> -BuBr	5.2.1.A	32
<i>n</i> -C ₈ H ₁₇ Br	5.2.1.C	75 ^b
PhCH ₂ Br	5.2.1.A	56 ^c
<i>N</i> -Alkylation of propanamide		
EtBr	5.2.1.B	51
<i>n</i> -PrBr	5.2.1.B	50
<i>n</i> -BuBr	5.2.1.B	54

^a 71% + 3% dialkylation using 5.2.1.C (15 min at 80°C). ^b with 4% dialkylation after 1 h at 60°C. ^c with 24% *N,N*-bisbenzyl derivative.

Method B: The haloalkane (0.06 mol) in PhH (10 ml) is added dropwise over *ca.* 1.5 h to a stirred mixture of the amide (0.05 mol), TBA-HSO₄ (1.7 g, 5 mmol), finely powdered NaOH (10 g) and K₂CO₃ (10 g) in PhH (60 ml) at 40–50°C. The mixture is stirred for a further 2.5 h under reflux and then cooled to room temperature and filtered. The solid is washed with PhH (3 × 20 ml) and the organic solutions are evaporated under reduced pressure to yield the *N*-alkylated amide.

Method C: The carboxamide (10 mmol), TBA-Br (96 mg, 0.3 mmol), and KOH (0.85 g) are intimately mixed for 15 min at room temperature. The alkylating agent (12.5 mmol) is added and the mixture is stirred at 60–80°C. CH₂Cl₂ (50 ml) is added to the cooled mixture, filtered, and evaporated to yield the mono-*N*-alkylated carboxamide.

Further *N*-alkylation of *N*-alkylcarboxamides always requires the more vigorous solid:liquid two-phase conditions [4–7], whereas it has generally been found [8, 9] that the more acidic *N*-aryl derivatives can be alkylated under the milder liquid:liquid conditions (Table 5.11). (It has been shown that, with sufficiently vigorous mixing of the two liquid phases, it is possible to *N*-methylate formanilides without recourse to a phase-transfer catalyst [8]).

5.2.2 Preparation of *N,N*-disubstituted carboxamides

Method A: The dialkylation of carboxamides using procedure 5.2.1.B with the amide (0.05 mol) and an excess of the alkylating agent (0.14 mol) under reflux for a period of 3.5 h produces the *N,N*-dialkylamide.

Method B: The haloalkane (0.75 mol) in PhH (10 ml) is added dropwise to a stirred suspension of the *N*-alkylamide (0.05 mol), TBA-HSO₄ (1.7 g, 5 mmol), powdered NaOH (7.0 g), and K₂CO₃ (14 g) in PhH (50 ml) under reflux. The mixture is stirred for a further 4 h and then cooled to room temperature and diluted with PhH (50 ml) and H₂O (50 ml). The organic phase is separated, washed with H₂O (2 × 40 ml), dried (MgSO₄), and evaporated to yield the *N,N*-dialkylamide.

Method C: A suspension of the *N*-alkylformamide (0.1 mol), powdered NaOH (14 g), K₂CO₃ (8.0 g), and TBA-HSO₄ (3.4 g, 10 mmol) in PhH (60 ml) is stirred vigorously at 35–40°C for 30 min. The temperature is raised to 60°C and the alkylating agent (0.2 mol of dialkyl sulphate or 0.1 mol of haloalkane) in PhH (40 ml) is added over a period of 1 h. Stirring is continued at 60–70°C for a further 4 h and the mixture is then cooled to room temperature. PhH (50 ml) is added and the mixture is filtered. The solid is washed with PhH (2 × 30 ml) and the combined organic solutions are washed with H₂O (2 × 20 ml), dried (MgSO₄), and evaporated under reduced pressure to yield the *N,N*-dialkylformamide.

Method D: The anilide (0.02 mol) and TEBA-Cl (0.45 g, 2 mmol) in PhH or PhMe (50 ml) and NaOH (4.0 g) in H₂O (4 ml) are stirred at room temperature for 25 min. An excess of the alkylating agent (0.025–0.08 mol) is added to the syrup and the mixture is stirred and heated for a further period of time (Table 5.11). The mixture is then cooled to room temperature, the organic phase is separated, washed with dilute HCl or H₂SO₄ (2M, 25 ml) and then with H₂O until neutral, dried (Na₂SO₄), and evaporated to yield the *N*-alkylanilide.

Method E: The *N*-alkylcarboxamide (10 mmol), KOH (1.1 g) and TBA-Br (96 mg, 0.3 mol) are intimately mixed at room temperature for 15 min and the alkylating agent

TABLE 5.11

Selected examples of the synthesis of *N,N*-disubstituted carboxamides

R ¹ CONHR ²		Alkylating agent	Reaction conditions	% yield
R ¹ = Ph	R ² = H	EtBr	5.2.2.A	84
		<i>n</i> -BuBr	5.2.2.A	93
		PhCH ₂ Br	5.2.2.A	92
Ph	Me	MeI	5.2.2.E (24 h)	75
		EtI	5.2.2.E (24 h)	74
		<i>n</i> -BuBr	5.2.2.E (2 h/80°C)	90
		Br(CH ₂) ₂ Br	5.2.2.E (2 h/80°C)	58
		EtBr	5.2.2.B	88
Ph	Et	<i>n</i> -BuBr	5.2.2.B	85
		PhCH ₂ Br	5.2.2.B	86
		Me ₂ SO ₄	5.2.2.C	95
Ph	Ph	Et ₂ SO ₄	5.2.2.C (80°C)	95
		<i>n</i> -PrBr	5.2.2.C (70°C)	92
		PhCH ₂ Cl	5.2.2.C (70°C)	92
		MeBr	5.2.2.C	44
H	<i>t</i> -Bu	<i>n</i> -BuBr	5.2.2.C	45
		PhCH ₂ Br	5.2.2.C	53
		MeBr	5.2.2.C	81
H	PhCH ₂	<i>n</i> -BuBr	5.2.2.C	48
		PhCH ₂ Br	5.2.2.C	44
		MeBr	5.2.2.C	44
H	cyclo-C ₃ H ₁₁	MeBr	5.2.2.C	85
		<i>n</i> -BuBr	5.2.2.C	73
		PhCH ₂ Br	5.2.2.C	80
H	Ph	Me ₂ SO ₄	5.2.2.D (60°C/30 min)	62
H	4-EtOC ₆ H ₄	Me ₂ SO ₄	5.2.2.D (60°C/25 min)	77
H	3-MeC ₆ H ₄	Et ₂ SO ₄	5.2.2.D (65°C/20 min)	59
Me	<i>t</i> -Bu	EtBr	5.2.2.B	20
Me	Ph	Me ₂ SO ₄	5.2.2.D (25°C/45 min)	84
		Et ₂ SO ₄	5.2.2.D (70°C/15 min)	90
		<i>n</i> -PrBr	5.2.2.D (70°C/3.5 h)	82
		<i>n</i> -BuI	5.2.2.D (80°C/22 h)	82
		Me(CH ₂) _n Br	5.2.2.D (108°C/1.5 h)	72 (<i>n</i> = 7)
			5.2.2.D (109°C/1 h)	61 (<i>n</i> = 11)
		PhCH ₂ Cl	5.2.2.D (80°C/2.5 h)	95
		CH ₂ =CHCH ₂ Br	5.2.2.D (95°C/15 min)	70
		Me ₂ SO ₄	5.2.2.D (35°C/45 min)	75
		Et ₂ SO ₄	5.2.2.D (93°C/15 min)	88
Me	4-EtOC ₆ H ₄	Me(CH ₂) _n Br	5.2.2.D (105°C/1 h)	83 (<i>n</i> = 7)
			5.2.2.D (106°C/1 h)	71 (<i>n</i> = 11)
		PhCH ₂ Cl	5.2.2.D (80°C/2.5 h)	95
Me	3-MeC ₆ H ₄	Me ₂ SO ₄	5.2.2.D (25°C/1 h)	75
		Me(CH ₂) ₇ Br	5.2.2.D (110°C/1 h)	49
		EtBr	5.2.2.B	73
Et	PhCH ₂	<i>n</i> -BuBr	5.2.2.B	82
		PhCH ₂ Br	5.2.2.B	96
		EtBr	5.2.2.B	17
<i>t</i> -Bu	Et	EtBr	5.2.2.B	17

(12 mmol) is then added. When the reaction is complete, CH_2Cl_2 (50 ml) is added and the mixture is filtered through Florosil. The filtrate is concentrated and chromatographed on silica to yield the dialkylcarboxamide.

The catalysed two-phase alkylation of carboxamides has the advantages of speed and simplicity over the traditional procedures and provides a valuable route to secondary and tertiary amines by hydrolysis or reduction of the amides, respectively. The procedure appears to be limited, however, to reactions with primary haloalkanes and dialkyl sulphates, as secondary haloalkanes are totally unreactive [6, 7]. The use of iodoalkanes should be avoided, on account of the inhibiting effect of the released iodide ion on the catalyst. Also, the *N*-alkylation reaction is generally susceptible to steric effects, as seen by the low yields in the *N*-ethylation of *N*-*t*-butylacetamide and of *N*-ethylpivalamide [6]. However, the low steric demand of the formyl group permits *N,N*-dialkylation and it is possible to obtain, after hydrolysis in 60% ethanolic sulphuric acid, the secondary amines having one (or, in some cases, two) bulky substituent(s) [7].

Trifluoroacetamide is mono- or di-*N*-alkylated under solid:liquid phase-transfer catalytic conditions, depending on the amount of alkylating agent and base used [10]. With the facile hydrolysis of the trifluoroacetamides, the procedure provides a convenient alternative to the Gabriel synthesis for alkylamines and also gives a high-yielding process for dialkylamines, either with identical or with different alkyl groups.

5.2.3 *N*-Alkylation of trifluoroacetamide (Table 5.12)

Method A. Monoalkylation: CF_3CONH_2 (11.3 g, 0.1 mol) in MeCN (100 ml) is stirred with the alkylating agent (0.05 mol), powdered K_2CO_3 (13.8 g) and TBA-Br (1.61 g, 5 mmol) at 50°C. When the reaction is complete, as shown by GLC analysis, the cooled mixture is filtered and the residue washed with CH_2Cl_2 (30 ml). The combined organic solutions are evaporated and the amine isolated by chromatography from silica.

Method B. Dialkylation: The *N*-substituted trifluoroacetamide (50 mmol), alkylating

TABLE 5.12

Selected examples of the alkylation of trifluoroacetamide and *N*-alkyltrifluoroacetamides

Amide	Method	Alkylating agent	Reaction time	% yield
CF_3CONH_2	5.2.3.A	<i>n</i> - $\text{C}_8\text{H}_{17}\text{Br}$	2 h	90
	5.2.3.A	PhCH_2Cl	14 h	69
	5.2.3.A	PhCH_2Br	2 h	73
	5.2.3.A	$\text{PhCH}=\text{CHCH}_2\text{Cl}$	6 h	59
	5.2.3.A	$\text{PhCH}=\text{CHCH}_2\text{Br}$	1 h	70
<i>n</i> - $\text{C}_8\text{H}_{17}\text{NHCOCF}_3$	5.2.3.B	<i>n</i> - $\text{C}_8\text{H}_{17}\text{OSO}_2\text{Me}$	72 h	50
	5.2.3.B	PhCH_2Br	60 h	65
$\text{PhCH}_2\text{NHCOCF}_3$	5.2.3.B	PhCH_2Cl	6 h	86
	5.2.3.B	PhCH_2Br	3 h	98
	5.2.3.B	MeI	48 h	63

agent (0.1 mol), K_2CO_3 (20.73 g) and TBA-Br (1.61 g, 5 mmol) are heated at 80°C until the reaction is complete, as shown by TLC analysis, and the dialkylamine is isolated as described in 5.2.3.A.

Alkylation of trifluoro- and trichloroacetamides with α -bromoacetic esters has been utilized for the synthesis of a wide range of α -aminoacetic acids [11–13] (Table 5.13). Hydrolysis of the intermediate α -trihaloacetamidoacetic esters with methanolic potassium hydroxide converts the methyl and ethyl esters directly into the amino carboxylic acids. *t*-Butyl α -aminoacetates are more stable, but they are hydrolysed under phase-transfer catalytic conditions (see Chapter 9.2). Reaction of the trihaloacetamides with 1,4-dibromobutane and 1,5-dibromopentane and subsequent hydrolysis provides a simple route to pyrrolidine-2-carboxylic acid (75%) and piperidine-2-carboxylic acid (58%) [11, 12].

TABLE 5.13

Selected examples of the synthesis of α -aminoacetic acids via the intermediate trifluoroacetamido derivatives

$R^1CHBrCO_2R^2$		Reaction time	% yield of trifluoroacetamidoacetic esters	% yield of α -amino acids ^a
$R^1 = H$	$R^2 = Et$	30 min	65	62
Me	Et	1 h	72	71
$PhCH_2$	Et	48 h	16	16
Ph	Et	20 min	70	64
2-MeC ₆ H ₄	Me	20 min	81	73
3-MeOC ₆ H ₄	Me	20 min	70	64

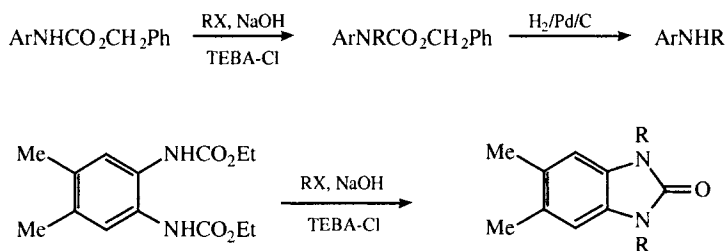
^a Overall yield from the α -bromoacetate after hydrolysis of the α -trifluoroacetamidoacetate with methanolic KOH.

5.2.4 Trihaloacetamidoacetic esters

Anhydrous K_2CO_3 (5.53 g, 40 mmol) is added to the trihaloacetamide (40 mmol), TEBA-Cl (0.46 g, 2 mmol) and the α -bromoacetic ester (20 mmol) in MeCN (40 ml) at room temperature. The mixture is stirred under reflux until the reaction is complete, as shown by TLC analysis. The mixture is cooled, filtered through Celite, and evaporated to yield the crude α -trihaloacetamidoacetate, which is purified by chromatography.

The efficient *N*-alkylation of the *N*-acylaminoarenes under solid:liquid phase-transfer catalytic conditions has been utilized for the specific synthesis of *N*-monoalkylaminoarenes [14, 15].

The analogous reaction of benzyl and butyl naphthylcarbamates and of benzyl phenylcarbamates has been carried out in good yield under both liquid:liquid and solid:liquid two-phase conditions, using benzyltriethylammonium chloride as the catalyst [16, 17]. A similarly catalysed *N*-alkylation of the ethyl carbamic esters derived from 1,2-diaminobenzene is reported [17] to lead to the formation of 1,3-dialkylbenzimidazol-3-ones (Scheme 5.7).



Scheme 5.7

5.2.5 *N*-Alkylation of *N*-acylaminoarenes

The acylaminoarene (20 mmol) is stirred with powdered NaOH (3.2 g, 80 mmol), anhydrous K_2CO_3 (27.6 g, 0.2 mol) and TBA- HSO_4 (0.136 g, 0.4 mmol) in PhMe (100 ml) for 30 min at 30–35°C. The alkylating agent (20 mmol) in PhMe (10 ml) is added dropwise over 30 min and the mixture is stirred for a further 1 h at 30–35°C. The filtered mixture is washed well with H_2O , dried (Na_2SO_4), and evaporated to yield the *N*-alkylated product.

Hydroxamic acids are *N*-alkylated (45–70%) under solid:liquid two-phase conditions under strongly basic conditions [18].

5.2.6 *N*-Alkylation of hydroxamic acids

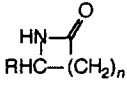
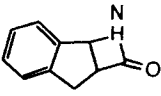
Aliquat (0.1 g, 0.25 mmol) is added to the hydroxamic acid (9 mmol) and *t*-BuOK (5 g, 45 mmol) and the mixture is stirred at 50°C for 2 h. The alkylating agent (45–50 mmol) is added and the mixture is stirred for a further 2 h at 50°C. The mixture is filtered and the filtrate evaporated to yield the *N*-alkylated product, which is purified by chromatography from silica.

N-Alkylation of lactams (Table 5.14) is generally best conducted under solid:liquid two-phase conditions [19–21] in order to prevent hydrolytic ring cleavage, although acceptable yields of the *N*-alkylated derivatives have also been obtained under liquid:liquid conditions, using a large excess of the alkylating agent [22]. It is interesting that, unlike the corresponding reactions with acyclic amides, the lactams are *N*-alkylated by secondary bromoalkanes in good yields, when the solid:liquid two-phase reaction is conducted in tetrahydrofuran [19, 20]. It is possible that similar conditions may permit the analogous alkylation of the acyclic amides.

5.2.7 *N*-Alkylation of lactams

Method A: The lactam (0.05 mol) and the bromoalkane (0.05 mol) in dry THF (20 ml) is added with stirring to powdered KOH (3.1 g) and TBA-Br (3.2 g, 10 mmol) in dry THF (50 ml) over a period of *ca.* 1 h at room temperature. The mixture is stirred for 3–7 h at room temperature (or refluxed for 2–3 h, if a chloroalkane is used). The mixture is then filtered and evaporated. CH_2Cl_2 (50 ml) and H_2O (50 ml) are added to the residue and the

TABLE 5.14
 Selected examples of the *N*-alkylation of lactams

Haloalkane	Method	% yield
 RHC(=O)NH_2 $n = 1, (R = \text{CH}=\text{CH}_2)$		
MeI	5.2.7.A	86
<i>n</i> -C ₆ H ₁₃ Br	5.2.7.A	90
<i>iso</i> -PrBr	5.2.7.A	45
<i>n</i> -C ₄ H ₉ CHBrMe	5.2.7.A	48
PhCH ₂ Cl or PhCH ₂ Br	5.2.7.A	84
I(CH ₂) ₄ Cl	5.2.7.A	77
4-MeOC ₆ H ₄ CH ₂ Cl	5.2.7.A	78
BrCH ₂ CO ₂ Et	5.2.7.A	70
BrCH ₂ CH(OMe) ₂	5.2.7.A	30
$n = 1, (R = \text{Ph})$		
<i>n</i> -C ₆ H ₁₃ Br	5.2.7.A	83
2-BrC ₆ H ₁₃	5.2.7.A	49
PhCH ₂ Cl	5.2.7.A	81
BrCH ₂ CO ₂ Et	5.2.7.A	70
$n = 2, (R = \text{H})$		
MeI	5.2.7.A (rt/3 h)	92
Me ₂ SO ₄	5.2.7.B (2 h)	53
<i>n</i> -BuCl	5.2.7.A (reflux/3 h)	90
<i>n</i> -BuBr	5.2.7.A (rt/3 h)	85
<i>sec</i> -BuBr	5.2.7.A (rt/7 h)	71
<i>n</i> -C ₈ H ₁₇ Br	5.2.7.B (4 h)	20
PhCH ₂ Br	5.2.7.A (rt/4 h)	89 ^a
Ph(CH ₂) ₂ Br	5.2.7.A (rt/5 h)	45
2-pyridyl(CH ₂) ₂ Cl	5.2.7.A (reflux/3 h)	45
NC(CH ₂) ₂ Cl	5.2.7.A (reflux/3 h)	71
(MeO) ₂ CH(CH ₂) ₂ Cl	5.2.7.A (reflux/3 h)	70
$n = 3, (R = \text{H})$		
MeI	5.2.7.A (rt/3 h)	95
<i>n</i> -BuCl	5.2.7.A (reflux/2 h)	85
<i>n</i> -BuBr	5.2.7.A (rt/4 h)	82
<i>sec</i> -BuBr	5.2.7.A (rt/7 h)	65
NC(CH ₂) ₂ Cl	5.2.7.A (reflux/3 h)	70
(MeO) ₂ CH(CH ₂) ₂ Cl	5.2.7.A (reflux/3 h)	69
$n = 4, (R = \text{H})$		
MeI	5.2.7.A (rt/3 h)	96
<i>n</i> -BuCl	5.2.7.A (reflux/3 h)	87
<i>n</i> -BuBr	5.2.7.A (rt/5 h)	79 ^b
<i>sec</i> -BuBr	5.2.7.A (rt/7 h)	66
PhCH ₂ Br	5.2.7.A (rt/4 h)	91 ^c
Ph(CH ₂) ₂ Br	5.2.7.A (rt/6 h)	38
$n = 6, (R = \text{H})$		
<i>n</i> -C ₁₂ H ₂₅ Br	5.2.7.B (50 h)	27 ^d
PhCH ₂ Br	5.2.7.B (5 h)	15 ^e
		
<i>n</i> -C ₆ H ₁₃ Br	5.2.7.A	70
2-BrC ₆ H ₁₃	5.2.7.A	65
PhCH ₂ Cl	5.2.7.A	33
BrCH ₂ CO ₂ Et	5.2.7.A	67

^a 66% after 5 h, using 5.2.7.C. ^b 73% after 30 h, using 5.2.7.B. ^c 55% after 5 h, using 5.2.7.B ^d 54% recovery of starting material. ^e 80% recovery of starting material.

organic phase is separated, washed with brine (2×25 ml), dried (MgSO_4), and evaporated to give the *N*-alkylated lactam.

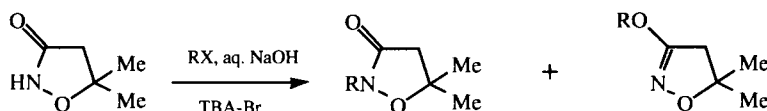
Method B: The alkylating agent (0.05 mol) is added dropwise to a stirred mixture of the lactam (0.05 mol) and TEBA-Cl (1.14 g, 5 mmol) in a two-phase system of PhH (50 ml) and aqueous NaOH (50%, 6 ml). The mixture is heated at $40\text{--}50^\circ\text{C}$ until TLC analysis indicates the completion of the reaction (Table 5.14). During the course of the reaction a further quantity of the alkylating agent (0.01–0.1 mol) is added. The organic phase is separated and the aqueous phase is extracted with PhH (20 ml). The combined organic solutions are washed with brine (15 ml), dried (MgSO_4), and evaporated to yield the *N*-alkylated lactam.

N-Substituted ureas are alkylated under solid:liquid phase-transfer catalytic conditions to yield the *N'*-alkylated products to the exclusion of *N*- and *O*-alkylated derivatives [23]. Surprisingly, *N*-aryl ureas do not react under similar conditions.

5.2.8 *N,N'*-Disubstituted ureas

The alkylating agent (20 mmol) is added to the *N*-substituted urea (20 mmol), NaOH (3.2 g), K_2CO_3 (0.55 g), and TBA-Cl (0.28 g, 1 mmol) in toluene (40 ml). The mixture is stirred under reflux until the reaction is complete (*ca.* 2 h) and then cooled, poured into H_2O (150 ml), and extracted with CHCl_3 (50 ml) and CH_2Cl_2 (50 ml). The organic solutions are washed with H_2O (50 ml), dried (Na_2SO_4), and evaporated to yield the disubstituted urea.

In contrast with the amides, which yield only *N*-alkylated products, the corresponding reaction of 5,5-dimethylisoxazolidin-3-one (Scheme 5.8) produces both the *N*- and *O*-alkylated derivatives [24] (Table 5.15). With the exception of the *sec*-bromobutane, the overall yields from primary and secondary haloalkanes are comparable, but there is a tendency for the secondary haloalkanes to produce slightly higher yields of the ethers.



Scheme 5.8

TABLE 5.15

Alkylation of 5,5-dimethylisoxazol-3-ones

Haloalkane	% yield	
	<i>N</i> -Alkylation	<i>O</i> -Alkylation
EtBr	59	19
<i>iso</i> -PrBr	35	22
<i>n</i> -BuBr	49	16
<i>sec</i> -BuBr	27	12
cyclo- $\text{C}_3\text{H}_7\text{Br}$	42	28
$\text{Ph}(\text{CH}_2)_2\text{Br}$	55	10
$\text{BrCH}_2\text{CO}_2\text{Me}$	60	15

5.2.9 Alkylation of 5,5-dimethylisoxazol-3-one

The haloalkane (0.01 mol) in PhH (50 ml) is added to the dimethylisoxazolone (1.1 g, 0.01 mol) and TBA-Br (0.13 g, 0.4 mmol) in aqueous NaOH (50%, 10 ml). the mixture is stirred at 55°C for 5 h and the organic phase is then separated, washed with H₂O (2 × 25 ml), dried (MgSO₄), and evaporated. The isomers are separated by HPLC.

The simplicity of the two-phase modification of the Gabriel synthesis of primary amines, via the *N*-alkylation of potassium phthalimide, makes the procedure considerably more convenient than the traditional method, which normally requires the use of anhydrous dipolar aprotic solvents. The reaction can be conducted under solid:liquid conditions using potassium hydroxide in toluene [25], or with preformed potassium phthalimide [26, 27] (*cf.* ref. 28). As is normal for acylation reactions, relatively mild conditions are required for the preparation of the *N*-ethoxycarbonyl derivative [29], whereas a reaction temperature of 100°C is generally used for *N*-alkylation (Table 5.16). The reaction time for the solid:liquid two-phase system can be reduced dramatically with retention of the high yields, when the reaction mixture is subjected to microwave irradiation [30].

5.2.10 Alkylation of phthalimide

Method A: Phthalimide (14.7 g, 0.1 mol), powdered KOH (6.7 g, 0.12 mol) and Aliquat (18 g, 25 mmol) in PhMe (25 ml) are stirred at room temperature for 2 h. The alkylating agent (0.1 mmol) is added dropwise and the mixture is then stirred at 100°C (Table 5.16). The cooled mixture is filtered and the solid washed with Et₂O (2 × 25 ml). The organic solutions are evaporated to yield the *N*-alkylphthalimide, which is purified by recrystallization from EtOH or by chromatography.

TABLE 5.16
Selected examples of *N*-substituted phthalimides

Alkylating agent	Method	Reaction time	% yield
<i>n</i> -BuBr	5.2.10.B	4 min	73
<i>sec</i> -BuBr	5.2.10.A	16 h	84
<i>n</i> -C ₅ H ₁₁ Br	5.2.10.B	4 min	90
<i>n</i> -C ₈ H ₁₇ Br	5.2.10.A	6 h	82 ^a
C ₆ H ₁₃ CHBrMe	5.2.10.A	16 h	82
<i>n</i> -C ₁₀ H ₂₁ Cl	5.2.10.B	4 min	51
<i>n</i> -C ₁₂ H ₂₅ I	5.2.10.B	10 min	95
<i>n</i> -C ₁₆ H ₃₃ Br	5.2.10.A	6 h	82
CH ₂ =CHCH ₂ Br	5.2.10.C	4 h	95 ^b
PhCH ₂ Cl	5.2.10.B	4 h	93 ^c
PhCH ₂ Br	5.2.10.A	4 h	86
BrCH ₂ CO ₂ Et	5.2.10.A	4 h	85
Br(CH ₂) ₂ Br	5.2.10.B	4 min	49 ^{d,e}
Br(CH ₂) ₂ Br	5.2.10.C	6 h	80
ClCO ₂ Et	5.2.10.A	4 h ^e	88

^a 85% using 5.2.10.C (6 h). ^b at 25°C. ^c 90% using 5.2.10.C (5 h). ^d *N*-(2-bromoethyl)phthalimide, 1,2-di(*N*-phthalimidyl)ethane is also obtained. ^e 80% using 5.2.10.C (6 h).

Method B: Phthalimide (0.7 g, 4.8 mmol), K_2CO_3 (2.6 g, 18.8 mmol), and TBA-Br (0.15 g, 0.45 mmol) in an excess of the haloalkane (6.0 mmol) are heated in an open beaker in a microwave oven (450 W) for *ca.* 4 min. The cooled mixture is then extracted with CH_2Cl_2 (2×25 ml). The dried ($MgSO_4$) extracts are evaporated to yield the *N*-alkylphthalimide.

Method C: The alkylating agent (1 mmol) is added to potassium phthalimide (0.185 g, 1 mmol) and TEBA-Br (32 mg, 0.1 mmol) at room temperature over a period of 1 h. The mixture is kept at $100^\circ C$ for 4–5 h. H_2O (5 ml) is added and the mixture is extracted with Et_2O (3×10 ml). The ethereal extracts are washed well with aqueous NaOH and H_2O , dried ($MgSO_4$), and evaporated to yield the *N*-alkylphthalimide.

In a similar manner, saccharin has been *N*-alkylated and *N*-acylated (Table 5.17) [31, 32]. There is good evidence that the kinetic *O*-alkylated product is initially formed and it is converted into the thermodynamically more stable *N*-alkyl derivative upon prolonged heating [31, 32]. The reaction fails with secondary haloalkanes and is most successful with primary bromoalkanes [31, 32].

TABLE 5.17
N-Alkylation and *N*-acylation of saccharin

Alkylating or acylating agent	Reaction conditions	% yield
MeI	$85^\circ C/20$ h	90
<i>n</i> -BuBr	$85^\circ C/20$ h	90
<i>iso</i> - $C_5H_{11}Br$	$85^\circ C/30$ h	80
<i>n</i> - $C_6H_{13}Br$	$85^\circ C/40$ h	85
<i>n</i> - $C_8H_{17}Br$	$85^\circ C/40$ h	85
<i>n</i> - $C_{12}H_{25}Br$	$100^\circ C/56$ h	85 ^a
<i>n</i> - $C_{18}H_{37}Br$	$105^\circ C/72$ h	80 ^a
$CH_2=CHCH_2Br$	$60^\circ C/6$ h	91
$PhCH_2Br$	$80^\circ C/6$ h	91
MeCOCl	$30^\circ C/45$ min	85
PhCOCl	$80^\circ C/45$ min	88
$CH_3(CH_2)_{12}COCl$	$80^\circ C/3$ h	90

^a 0.12 g (0.38 mmol) of catalyst used.

5.2.11 *N*-Alkylation and *N*-acylation of saccharin

Powdered sodium saccharin (0.49 g, 2.4 mmol), the alkylating or acylating agent (2 mmol), and TBA-Br (60 mg, 0.19 mmol) in PhMe (10 ml) are heated with stirring until TLC analysis indicates the complete consumption of the alkylating (acylating) agent. The mixture is then cooled to room temperature and filtered. The solid residues are washed with PhMe (2×25 ml) and the combined organic solutions are evaporated. The product can be purified by chromatography from silica gel, using $CHCl_3$ as the eluent.

Intramolecular alkylation of the amides of ω -halocarboxylic acids, under phase-transfer catalysed conditions, provides an excellent route to lactams. The procedure

is not ideal for the synthesis of aziridones (α -lactams) [33, 34], but aziridones [34–38], pyrrolid-2-ones and piperid-2-ones [33] have been synthesized using liquid:liquid two-phase conditions in acceptable yields (70–90%) under relatively mild conditions with either a quaternary ammonium salt or a polymer-supported catalyst. Intramolecular cyclization to form the seven-membered ring is more difficult and the *N*-phenyl compound has been obtained only after a reaction time of

TABLE 5.18
Cyclization of β -halocarboxamides

$\begin{array}{c} \text{R}^1 \quad \text{R}^2 \\ \quad \\ \text{X}-\text{CH}-\text{C}-\text{CONHR}^4 \\ \\ \text{R}^3 \end{array}$				$\begin{array}{c} \text{R}^2 \\ \\ \text{R}^1-\text{CH}-\text{C}-\text{R}^2 \\ \quad \\ \text{R}^4-\text{N}-\text{C}=\text{O} \end{array}$		
R ¹	R ²	R ³	R ⁴	X	Method	% yield
H	H	H	4-NO ₂ C ₆ H ₄	Br	5.2.12.B ^a	81
H	H	H	4-ClC ₆ H ₄	Br	5.2.12.B ^a	94
H	H	H	Ph	Br	5.2.12.B ^b	94 ^c
H	H	H	Ph	Cl	5.2.12.A(70 h) ^d	5 ^e
H	H	H	4-MeOC ₆ H ₄	Br	5.2.12.B ^b	92
H	H	H	1-naphthyl	Br	5.2.12.B ^a	91
H	H	H	PhCH ₂	Br	5.2.12.B ^b	86
H	H	H	PhCH ₂	Cl	5.2.12.A(100 h) ^d	trace ^f
H	H	H	4-MeOC ₆ H ₄ CH ₂	Br	5.2.12.B ^a	88
H	H	H	Ph(CH ₂) ₂	Br	5.2.12.B ^b	83
H	H	H	<i>n</i> -Pr	Br	5.2.12.B ^b	67
H	H	H	<i>cyclo</i> -C ₆ H ₁₁	Br	5.2.12.B ^e	74 ^h
H	H	H	CH ₂ CO ₂ Et	Br	5.2.12.B ^a	85
H	H	H	CH(Me)CO ₂ Me	Br	5.2.12.B ^a	84
H	H	H	CH(CH ₂) ₂ CO ₂ Me	Br	5.2.12.B ^a	87
H	Me	Me	Ph	Cl	5.2.12.A (9 h) ^{d,i,j}	96
H	Me	Me	PhCH ₂	Cl	5.2.12.A (80 h) ^{d,i}	91
H	Me	Br	Ph	Br	5.2.12.A (4 h) ^{d,i}	95
H	Me	Br	PhCH ₂	Br	5.2.12.A (100 h) ^{d,i,j}	93
COPh	H	H	Ph	Br	5.2.12.B ^a	60
COPh	H	H	4-MeOC ₆ H ₄	Br	5.2.12.B ^a	52
COPh	H	H	4-MeC ₆ H ₄	Br	5.2.12.B ^a	56
COPh	H	H	4-ClC ₆ H ₄	Br	5.2.12.B ^a	61
$\begin{array}{c} \text{Me} \\ \\ [\text{BrCH}_2-\text{C}-\text{CONH}]_2-\text{R} \\ \\ \text{Br} \end{array}$				$\left[\begin{array}{c} \text{Me} \\ \\ \text{Br}-\text{C}-\text{CH}_2 \\ \quad \\ \text{C}-\text{N}-\text{R} \\ \quad \\ \text{O} \quad \text{O} \end{array} \right]_2$		
R = 1,2-C ₆ H ₄				5.2.12.B (3 h) ^j		97
1,3-C ₆ H ₄				5.2.12.B (3 h) ^j		95
1,4-C ₆ H ₄				5.2.12.B (1 h) ^j		98
(1,4-C ₆ H ₄)SO ₂ (1,4-C ₆ H ₄)				5.2.12.B (1 h) ^j		89

^a Solvent: CH₂Cl₂:MeCN (19:1). ^b Solvent: CH₂Cl₂ c 5% azetidone and 58% *N*-phenylacrylamide under liquid:liquid two-phase conditions. ^d Using Duolite A-109 (Cl⁻ form). ^e 64% piperazine-2,5-dione after 18 h. ^f 88% piperazine-2,5-dione. ^g Solvent: THF. ^h 63% yield in CH₂Cl₂:MeCN. ⁱ Solvent: PhH. ^j Using TEBA-Cl.

95 hours whereas, even after 150 hours, the *N*-alkyl carboxamides failed to cyclize [34].

Azetidones (β -lactams) are generally obtained in high yield from β -halopropionamides (Table 5.18) and the low yield from the reaction of *N*-phenyl β -chloropropionamide can be reconciled with the isolation of *N*-phenyl acrylamide in 58% yield [34]. The unwanted elimination reaction can be obviated by conducting the cyclization in a solid:liquid system under high dilution [35, 36]. Azetidones are also formed by a predominant intramolecular cyclization of α,β -dibromopropionamides [34], in preference to intermolecular dimerization to yield piperazine-2,5-diones, or intramolecular alkylation to yield aziridones. A one-pot formation of azetidones in 45–58% yield from the amine and β -bromocarboxylic acid chloride has also been reported [38].

In contrast, liquid:liquid phase-transfer catalysis is virtually ineffective for the conversion of α -bromoacetamides into aziridones (α -lactams). Maximum yields of only 17–23% have been reported [31, 32], using tetra-*n*-butylammonium hydrogen sulphate or benzyltrithylammonium bromide over a reaction time of 4–6 days. It is significant that a solid:liquid two-phase system, using solid potassium hydroxide in the presence of 18-crown-6 produces the aziridones in 50–94% yield [33], but there are no reports of the corresponding quaternary ammonium ion catalysed reaction. Under the liquid:liquid two-phase conditions, the major product of the reaction is the piperazine-2,5-dione, resulting from dimerization of the bromoacetamide [34, 38]. However, only moderate yields are isolated and a polymer-supported catalyst appears to provide the best results [34, 38]. Significant side reactions result from nucleophilic displacement by the aqueous base to produce hydroxyamides and ethers.

5.2.12 Synthesis of azetidones

Method A: The β -halopropionamide (10 mmol) and TEBA-Cl* (0.11 g, 0.5 mmol) in PhH or CH_2Cl_2 (20 ml) and aqueous NaOH (50%, 10 ml) are stirred at room temperature for 4–100 h. H_2O is then added and the organic phase is separated. The aqueous phase is extracted with CH_2Cl_2 (2×10 ml) and the combined organic solutions are washed with H_2O (2×20 ml), dried (Na_2SO_4), and evaporated. [* Duolite A-109 (Cl^- form) can also be used. It should be removed by filtration from the reaction mixture before work-up.]

Method B: The β -bromopropionamide (5 mmol) in CH_2Cl_2 or a CH_2Cl_2 : MeCN (19 : 1) mixture (100 ml) is added slowly with stirring at room temperature to powdered KOH (0.34 g, 6 mmol) and TBA-Br (0.32 g, 1 mmol) in the same solvent (100 ml) over a period of 6 h. The mixture is stirred for a further 30 min and then filtered. The solids are washed with CH_2Cl_2 (2×15 ml) and the organic solutions are concentrated and chromatographed on silica to yield the azetidine.

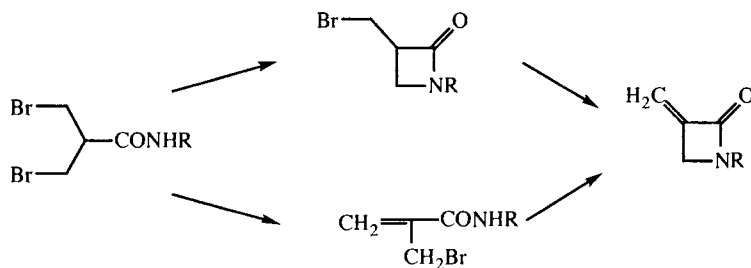
3-Methyleneazetidones have been obtained [39, 40] under liquid:liquid and solid:liquid basic conditions (Table 5.19) from an intramolecular cyclization and elimination reaction of 3-bromo-2-(bromomethyl)propionamides (Scheme 5.9). Traditional methods for the preparation of such compounds are either not particularly adaptable for general use, or involve lengthy and vigorous reaction conditions. In

TABLE 5.19
Selected examples of the synthesis of 3-methyleneazetidones

<i>N</i> -substituent	Method	% yield
Et	5.2.13.A	18
PhCH ₂	5.2.13.B	76
2-FurylCH ₂	5.2.13.B	80
3,4-(MeO) ₂ C ₆ H ₃ CH ₂	5.2.13.B	84
3-PyridylCH ₂	5.2.13.C	23
(MeO) ₂ CHCH ₂	5.2.13.C	43
<i>iso</i> -Bu	5.2.13.A	56
cyclo-C ₆ H ₁₁	5.2.13.A	40
1-C ₁₀ H ₁₅ ^a	5.2.13.C	40
4-NO ₂ C ₆ H ₄	5.2.13.A	83
4-CNC ₆ H ₄	5.2.13.A	76
3-Me ₂ NCOC ₆ H ₄	5.2.13.B	65
2,6-Cl ₂ C ₆ H ₃	5.2.13.A	78
2,4,6-Br ₃ C ₆ H ₂	5.2.13.A	82
Ph	5.2.13.A	86
4-MeC ₆ H ₄	5.2.13.A	96
3-Pyridyl	5.2.13.C	25

^a adamantyl.

contrast, in a liquid:liquid two-phase system, the *N*-aryl-3-methyleneazetidones are isolated in high yield (>80%) under relatively mild conditions. The yields for the corresponding preparation of the *N*-alkyl derivatives are generally lower (18–56%). Two reaction routes appear to be operative: the intermediate *N*-phenyl-3-bromomethylazetidone can be isolated in 65% yield, when the reaction time is reduced to 30 minutes, whereas low yields of the *N*-alkyl derivatives are accompanied by the formation of *N*-alkyl-3-bromomethylacrylamides, which have been shown to be precursors of the 3-methyleneazetidones under the phase-transfer catalytic conditions [40]. The intermediate acrylamides also dimerize under the basic conditions to yield derivatives of 1,5-diazacyclo-octa-2,6-dione [39].



Scheme 5.9

The methyleneazetidones are also obtained directly from the propionyl chlorides and the appropriate amine under basic conditions [39].

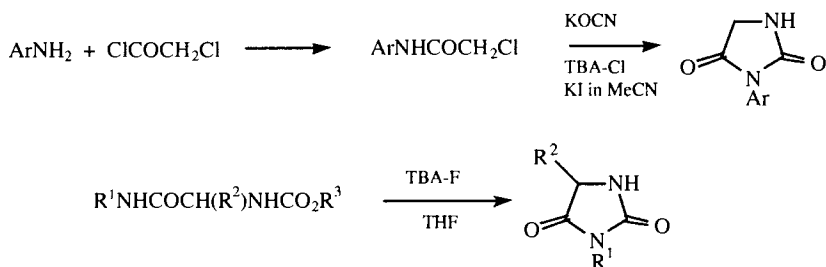
5.2.13 Synthesis of 3-methyleneazetidones

Method A: Using procedure 5.2.12.A, the 3-bromo-(2-bromomethyl)propionamide is stirred in aqueous NaOH (40%) and CCl_4 (or CH_2Cl_2) in the presence of TEBA-Br or TEPA-Br for 18 h at room temperature to produce the azetidone.

Method B: Powdered KOH (1.3 g) is added with stirring to the dibromopropionamide (7.7 mmol) and TBA-Br (0.26 g, 0.8 mmol) in CH_2Cl_2 (50 ml) over a period of 30 min and the mixture is stirred for a further 3 h at room temperature. The mixture is filtered and the solids are washed with CH_2Cl_2 (2×25 ml). The combined organic solutions are concentrated and the residue subjected to chromatography on silica.

Method C: The amine (50 mmol) is added to a stirred suspension of powdered KOH (16.8 g) and TBA-Br (1.61 g, 5 mmol) in CH_2Cl_2 (100 ml). $(\text{BrCH}_2)_2\text{CHCOCl}$ (13.2 g, 50 mmol) in CH_2Cl_2 (50 ml) is then added dropwise over a period of 30 min at room temperature. The mixture is stirred for a further 1 h and worked up by the procedure described in 5.2.13.B.

A phase-transfer catalysed nucleophilic displacement reaction on chloroacetanilides by cyanate ions, followed by ring-closure (Scheme 5.10), provides a simple and viable synthesis of hydantoins [41]. The formation of the hydantoins is inhibited by substituents in the *ortho*-position of the aryl ring, but the addition of potassium iodide, or tetra-*n*-butylammonium iodide, generally increases the overall rate of formation of the cyclic compounds, presumably by facilitating the initial nucleophilic substitution step.



Scheme 5.10

It is also possible to effect the cyclization of alkoxy carbonyl glycine amides to yield hydantoins (Scheme 5.10) using an excess of tetra-*n*-butylammonium fluoride, which acts as a basic catalyst [42]. The procedure has been extended to a range of *N*-alkoxy carbonyl peptides.

5.2.14 Preparation of hydantoins

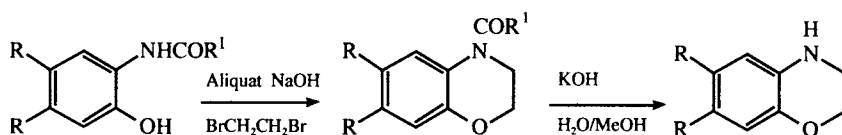
KI* (0.5 g) and TBA-Cl (50 mg, 0.22 mmol) are added with stirring to the chloroacetanilide (0.01 mol) and KOCN (0.8 g, 0.01 mol) in MeCN (50 ml) and the solution is stirred for 4–10 h at 60–80°C. The mixture is cooled to room temperature and evaporated under reduced pressure. The residue is washed with H_2O (2×50 ml) and extracted

with MeOH (3×25 ml). Evaporation of the MeOH yields the hydantion. [* Preformed TBA-I (0.1 g) may be used in place of the KI and TBA-Cl.]

5.2.15 Fluoride ion catalysed cyclization of *N*-benzyloxycarbonyl glycnamides

The glycnamide (13.5 mmol) and TBA-F \cdot 3H $_2$ O (12.6 g, 40 mmol) in THF (200 ml) are heated under reflux for 14 h. The solution is then concentrated and H $_2$ O (100 ml) is added to precipitate the hydantoin.

Alkylation of 2-hydroxyanilides with 1,2-dibromoethane under solid:liquid phase-transfer catalytic conditions leads to the formation of *N*-acyl 3,4-dihydro-2*H*-1,4-benzoxazines (Scheme 5.11) and optimum yields are obtained when a mixed organic phase of acetonitrile:dichloromethane (4:6) is used [43]. No reaction occurs in dichloromethane and a complex mixture of products results, when acetonitrile is used alone.



Scheme 5.11

5.2.16 Synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines

The hydroxyanilide (10 mmol), powdered NaOH (1.6 g), Br(CH $_2$) $_2$ Br (7.52 g, 40 mmol) and Aliquat (0.41 g, 21 mmol) in MeCN (32 ml) and CH $_2$ Cl $_2$ (48 ml) are stirred under N $_2$ at 25–30°C for 24 h. A second amount of powdered NaOH (0.4 g) is added and stirring is continued for a further 2 h. The mixture is filtered and the residue is washed with Et $_2$ O (2 \times 25 ml). The combined organic solutions are concentrated and the crude product is purified by chromatography from silica.

The acidities of sulphonamides are considerably greater than those of the carboxamides and, as a consequence, their *N,N*-dialkylation proceeds extremely easily [3]. Generally, use is made of a basic solid:liquid two-phase system and yields are usually greater than 80%, except when secondary bromoalkanes are used (Table 5.20). *N*-Monoalkylated sulphonamides have been obtained (85–98%) using a polymer-supported catalyst [44].

Alkylation of sulphamic esters under phase-transfer catalytic conditions (Table 5.21) is also generally superior to many of the alternative traditional procedures, but 'self alkylation' can occur with the methyl sulphamates, e.g. a mixture of methyl *N*-ethyl-*N*-phenylsulphamate and methyl *N*-methyl-*N*-phenylsulphamate is obtained when methyl *N*-phenylsulphamate is reacted with iodoethane [45]. The less acidic *N*-alkylsulphamates require more strongly basic conditions than do the corresponding *N*-phenyl derivatives.

TABLE 5.20
N,N-Dialkylation of sulphonamides

RSO ₂ NH ₂	Alkylating agent	% yield
R = Me	EtBr	76
	<i>iso</i> -PrBr	16
	PhCH ₂ Br	84
Ph	Me ₂ SO ₄	82
	EtBr	94
	<i>iso</i> -PrBr	10
	<i>n</i> -BuBr	88
	PhCH ₂ Br	78

 TABLE 5.21
N-Alkylation of sulphamic esters

R ¹ NHSO ₂ OR ²		Alkylating agent	Method	% yield
R ¹ = Ph	R ² = Et	Mel	5.2.19.A/5 min	91
		EtI	5.2.19.A/40 min	44
Ph	<i>n</i> -Pr	<i>n</i> -PrBr	5.2.19.A/15 h	80
		PhCH ₂ Cl	5.2.19.A/1 h	99
		Cl(CH ₂) ₃ Br	5.2.19.A/2 h	86
Ph	cyclo-C ₆ H ₁₁	<i>n</i> -C ₅ H ₁₁ Br	5.2.19.A/18 h	88
		PhCH ₂ Cl	5.2.19.A/45 min	88
		CH ₂ =CHCH ₂ Br	5.2.19.A/40 min	98
PhCH ₂	PhCH ₂	Mel	5.2.19.B/3 min	75
cyclo-C ₆ H ₁₁	cyclo-C ₆ H ₁₁	Mel	5.2.19.B/15 min	75
		CH ₂ =CHCH ₂ Br	5.2.19.B/23 h	87

Doubt has been cast on whether the acylation and sulphonylation of sulphamic esters (Table 5.22) proceeds via a phase-transfer mechanism. The rates of the reactions are enhanced and the reproducibility is increased by the addition of a catalyst, but yields in excess of 75% can be readily attained over an extended reaction time in the absence of the catalyst [46].

5.2.17 *N,N*-Dialkylation of sulphonamides

The alkylating agent (0.11 mol) is added with stirring to the sulphonamide (0.05 mol), powdered KOH (7.0 g), K₂CO₃ (7.0 g), and TBA-HSO₄ (1.7 g, 5 mmol) in PhH (60 ml) at room temperature. The mixture is stirred at *ca.* 50°C for 3–4 h and then cooled to room temperature and filtered. The solid residue is washed with PhH (3 × 20 ml) and the combined PhH solutions are washed with H₂O until neutral, dried (MgSO₄), and evaporated to yield the alkylated sulphonamide.

TABLE 5.22

N-Acylation and *N*-sulphonylation of sulphamate esters

PhNHSO ₂ OR	Acylation agent	Solvent	Addition time	Total reaction time	% yield
R = <i>n</i> -C ₆ H ₁₁	MeCOCl	CCl ₄	10 min	12 min	97
cyclo-C ₆ H ₁₁	MeCOCl	CCl ₄	10 min	20 min	71
	PhCOCl	CH ₂ Cl ₂	12 min	14 min	86
	(EtCO) ₂ O	CH ₂ Cl ₂	9 min	10 min	70
	MeSO ₂ Cl	CH ₂ Cl ₂	15 min	20 min	48
	TosCl	CH ₂ Cl ₂	10 min	12 min	83
	PhSO ₂ Cl	CH ₂ Cl ₂	8 min	11 min	67
	4-ClC ₆ H ₄ SO ₂ Cl	CH ₂ Cl ₂	8 min	14 min	47
	4-BrC ₆ H ₄ SO ₂ Cl	CH ₂ Cl ₂	12 min	15 min	64

5.2.18 Polymer-supported *N*-monoalkylation of sulphonamides

Duolite A-101D [Cl[−] form] is washed with an aqueous solution of the sodium salt of the sulphonamide, obtained by the dissolution of the sulphonamide in aqueous NaOH (0.5 M, 100 ml). The resin is washed repeatedly with H₂O, EtOH and MeCOMe and dried over P₂O₅ for 12 h. The resin (5 g) is then shaken with the alkylating agent (5 mmol) in EtOH (20 ml) at room temperature. The mixture is filtered and the filtrate evaporated to yield the *N*-monoalkylated product.

5.2.19 *N*-Alkylation of sulphamic esters

Method A: The sulphamic ester (2 mmol), anhydrous Na₂CO₃ (3.2 g), TEBA-Cl (0.37 g, 2 mmol), and the alkylating agent (7 mmol) are stirred at room temperature. When TLC analysis indicates the completion of the reaction, *n*-C₆H₁₄ (50 ml) is added and the mixture is stirred and filtered. Evaporation of the filtrate yields the *N*-alkylated sulphamate.

Method B: The sulphamic ester (2 mmol), powdered NaOH (0.8 g), K₂CO₃ (2.0 g), TEBA-Cl (0.37 g, 2 mmol), and the alkylating agent (7 mmol) are stirred at room temperature and the *N*-alkylated product is isolated by the procedure described in 5.2.19.A.

5.2.20 *N*-Acylation and sulphonylation of sulphamic esters

K₂CO₃ (1.0 g), NaOH (0.13 g), TEBA-Cl (50 mg, 0.2 mmol) and the sulphamic ester (2 mmol) in CH₂Cl₂ or CCl₄ (6 ml) are cooled to 0°C. The acyl (or sulphonyl) chloride (2.2 mmol) in CH₂Cl₂ or CCl₄ (3 ml) is added dropwise to the stirred mixture over a period of 8–15 min. When TLC analysis indicates that the reaction is complete, *n*-C₆H₁₄ (25 ml) is added and the product is isolated by the procedure described in 5.2.19.A.

A disadvantage of the traditional synthesis of *N*-alkyl-*N*-tosylhydrazones, particularly in the reaction of the tosylhydrazine with weakly electrophilic carbonyl compounds, is the instability of the hydrazine under the reaction conditions. However, *N*-alkylation of the tosylhydrazone (Table 5.23) under weakly basic condi-

TABLE 5.23
 Selected examples of the alkylation of *N*-tosylhydrazones

R ¹ R ² C=N.NHTos		Haloalkane	Reaction time	% yield
R ¹ = <i>t</i> -Bu	R ² = H	MeI	1 h	98
PhCH=CH	H	MeI	21 h	98
<i>n</i> -Pr	<i>n</i> -Pr	MeI	1 h	90
	-(CH ₂) ₄	MeI	6 h	66
PhCH ₂	PhCH ₂	MeI	5 h	92
Ph	Me	MeI	8 h	92
		EtI ^a	18 h	96
		PhCH ₂ Br	5 h	82
Ph	PhCH ₂	MeI	14 h	90
2-MeOC ₆ H ₄	PhCH=CH	MeI	5 h	97

^a 4-fold excess of EtI used

tions in the presence of a quaternary ammonium catalyst provides a useful mild alternative procedure [47].

5.2.21 *N*-Alkylation of *N*-tosylhydrazones

Aqueous NaOH (15%, 15 ml), the alkylating agent (6.94 mmol) and TPA-Cl (19 mg, 0.35 mmol) are added to a stirred solution of the *N*-tosylhydrazone (3.5 mmol) in CH₂Cl₂ (15 ml) at room temperature. The mixture is stirred at room temperature (Table 5.23) and the organic phase is then separated, washed with H₂O (2 × 20 ml), dried (Na₂SO₄), and evaporated under reduced pressure to yield the *N*-alkylated derivative.

The catalysed *N*-alkylation of the potassium salt of sulfoximines in 1,2-dimethoxyethane produces yields in excess of 90% [48]. Similarly, azacrown ethers have been synthesized by alkylation of bis(tosylamino)alkyl ethers under catalysed basic two-phase conditions [49] (Scheme 5.12). The yields of the cyclic products (Table 5.24) are influenced by the choice of the alkali metal hydroxide employed, suggesting that there is a degree of template control in the ring closure step. This is not the case in the analogous reaction of *p*-toluenesulphonamide with α, ω-dihaloalkanes [50], which leads to the formation of a mixture of 1:1 and 2:2 cyclic products

 TABLE 5.24
 Synthesis of azocrown ethers from bis-sulphonamides and α,ω-dibromoalkanes

TosNHCH ₂ (CH ₂ XCH ₂) _m CH ₂ NHTos		BrCH ₂ (CH ₂ OCH ₂) _n CH ₂ Br	% yield
<i>m</i> = 1	X = O	<i>n</i> = 1	82 ^{a,b}
1	O	2	77 ^c
2	O	2	80 ^{c,d}
1	NTos	1	83 ^{a,e}
1	NTos	2	80 ^a

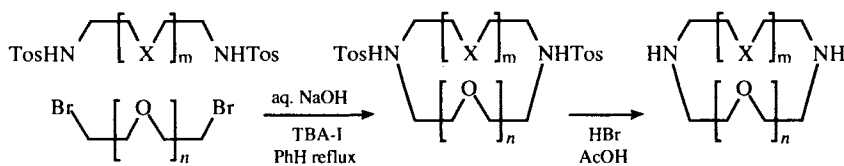
^a Using LiOH. ^b 58%, using NaOH. ^c Using NaOH. ^d 54%, using KOH. ^e 65%, using NaOH.

TABLE 5.25
Reaction of *p*-toluenesulphonamides with α,ω -dibromoalkanes

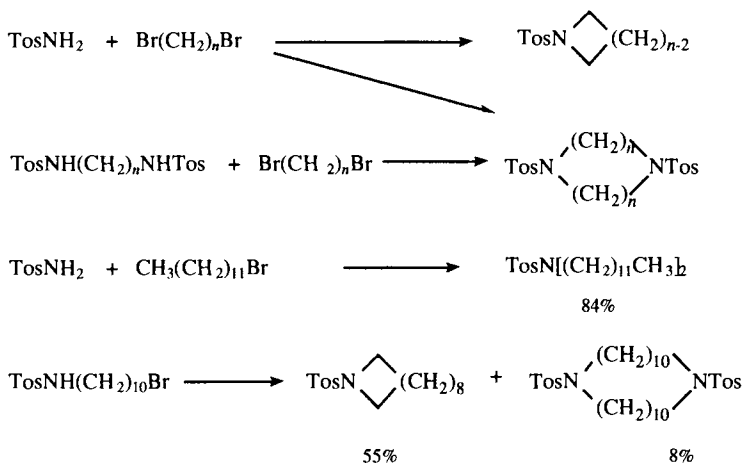
Br(CH ₂) _n Br	% yield	
	1 : 1 product	2 : 2 product
<i>Reaction with TosNH₂</i>		
<i>n</i> = 10	30	43
= 12 ^a	52	5
= 20	71	0
<i>Reaction with TosNH(CH₂)_mNHTos</i>		
<i>n</i> = 10 <i>m</i> = 10	0	50
= 11 = 11	0	48
= 12 = 12	0	62
= 20 = 20	0	55

^a Reaction of I(CH₂)₁₂I with TosNH₂ gives 49% of the 1:1 product and 19% of the 2:2 product.

(Table 5.25). Diazacycloalkanes are also obtained from the reaction of α,ω -dibromoalkanes with the bis(tosylamino)alkanes, whereas intermolecular reaction of 1-bromo-10-tosylaminodecane yields both 1:1 and 2:2 cyclic products (55% and 8%) under the basic conditions (Scheme 5.13). The reaction of *p*-toluenesulphonamide with *n*-bromododecane yields the di-*N*-alkylated sulphonamide (84%) [50].



Scheme 5.12



Scheme 5.13

5.2.22 Synthesis of azacrown ethers

The bis-sulphonamide (0.02 mol) and the α,ω -dibromo compound (0.02 mol) in PhH (or PhMe) (600 ml) are added to a refluxing two-phase system of aqueous NaOH (7.5%, 100 ml) and PhH (or PhMe) (100 ml) containing TBA-I (1.85 g, 5 mmol). The mixture is stirred under reflux for 8–10 h and then cooled to room temperature. The organic phase is separated, dried (MgSO_4), and evaporated to yield the *N*-tosyl azacrown ether which, upon treatment with acid, is converted into the azacrown ether.

5.2.23 Synthesis of diazacycloalkanes and related compounds

Method A: The bis(tosylamino)alkane (10 mmol) and the dibromoalkane (10 mmol) in PhH (500 ml) are added to a refluxing two-phase system of PhH (200 ml) and aqueous NaOH (2.5%, 100 ml), containing TBA-I (1.85 g, 5 mmol). The system is refluxed for 12 h and then cooled to room temperature. The organic phase is separated, dried (MgSO_4), and evaporated to yield the cyclic products, which are purified by chromatography on Kieselgel.

Method B: The tosylamino compound (0.05 mol), NaOH (4.0 g), the dihaloalkane (0.05 mol) and TBA-I (1.85 g, 5 mmol) in PhH (500 ml) and H_2O (20 ml) are stirred vigorously under reflux for 24 h. The system is cooled to room temperature and the organic phase is separated. The aqueous phase is extracted with CHCl_3 (2×50 ml) and the combined organic solutions are washed with H_2O (2×100 ml), dried (Na_2SO_4), and evaporated. The products are purified by chromatography from Kieselgel.

In a useful variant of the Gabriel synthesis of primary amines, diphenylphosphinamides have been *N*-alkylated under phase-transfer catalytic conditions (Table 5.26). The alkylation is carried out either directly using primary or secondary bromoalkanes [51, 52], or with alkyl methanesulphonates, produced *in situ* from methanesulphonyl chloride and the appropriate alcohol [53]. Mono- and dialkylation of diphenylphosphinamide is only accomplished in high yield under liquid:liquid two-phase conditions with reactive primary bromoalkanes; secondary bromoalkanes require the more vigorous solid:liquid conditions. However, the more acidic phosphinanilides can be alkylated by both primary and secondary bromoalkanes in a liquid:liquid two-phase system [49].

5.2.24 Synthesis of *N*-alkylphosphinamides

Method A: The bromoalkane (20 mmol) in PhH is added dropwise over 1.5 h with stirring to Ph_2PONH_2 (4.34 g, 20 mmol), TBA- HSO_4 (0.34 g, 1 mmol), aqueous NaOH (50%, 50 ml) and PhH (50 ml). The stirred mixture is refluxed for 1.5 h and then cooled to room temperature and diluted with PhH (50 ml). H_2O (50 ml) is added and the organic phase is separated. The aqueous phase is extracted with PhH (25 ml) and the organic solutions are then washed with H_2O until neutral, dried (MgSO_4), and evaporated to yield the *N*-alkylated derivative.

Method B: The bromoalkane (12 mmol) in PhH (25 ml) is added dropwise over a period of 1 h with stirring to a refluxing mixture of the Ph_2PONH_2 (2.17 g, 10 mmol), powdered NaOH (1.6 g), K_2CO_3 (6.9 g), and TBA- HSO_4 (0.34 g, 1 mmol) in PhH (50 ml). The

TABLE 5.26
N-Alkylation of phosphinamide and phosphinanilide

Alkylating agent	Method	% yield
<i>Alkylation of the phosphinamide (Ph₂PONH₂)</i>		
EtBr	5.2.24.A	80
EtOH	5.2.24.C	65
<i>n</i> -PrBr	5.2.24.A	78
<i>n</i> -PrOH	5.2.24.C	55
<i>iso</i> -PrBr	5.2.24.B	60
<i>iso</i> -PrOH	5.2.24.C	45
<i>n</i> -BuBr	5.2.24.A	91
<i>n</i> -BuOH	5.2.24.C	51
<i>sec</i> -BuBr	5.2.24.B	48
<i>sec</i> -BuOH	5.2.24.C	45
2-BrC ₃ H ₁₁	5.2.24.B	44
2-HOC ₃ H ₁₁	5.2.24.C	27
3-BrC ₆ H ₁₃	5.2.24.B	38
CH ₂ =CHCH ₂ Br	5.2.24.A	91
CH ₂ =CHCH ₂ OH	5.2.24.C	43
PhCH ₂ Br	5.2.24.A	45
PhCH ₂ OH	5.2.24.C	52
<i>Alkylation of the phosphinanilide (Ph₂PONHPh)</i>		
<i>iso</i> -PrBr	5.2.24.D	89
<i>sec</i> -BuBr	5.2.24.D	59
2-BrC ₃ H ₁₁	5.2.24.D	76
PhCH ₂ CH ₂ Br	5.2.24.D	81

refluxing mixture is stirred for a further 2 h and then cooled to room temperature. PhH (50 ml) is added and the *N*-alkylated derivative is isolated using the procedure described in 5.2.24.A.

Method C: MeSO₂Cl (3.4 g, 30 mmol) in PhH (30 ml) is added dropwise over 1 h with stirring to a refluxing mixture of Ph₂PONH₂ (4.34 g, 20 mmol), powdered NaOH (4.9 g), K₂CO₃ (8.3 g), TBA-HSO₄ (1.45 g, 4 mmol) and the appropriate alcohol (30 mmol) in PhH (50 ml). The mixture is stirred for a further 1 h under reflux and then cooled to room temperature and worked up using the procedure described in 5.2.24.A.

Method D: Ph₂PONHPh (2.93 g, 10 mmol), the bromoalkane (20 mmol), TBA-HSO₄ (17 g, 5 mmol), PhH (50 ml) and aqueous NaOH (50%, 50 ml) are stirred under reflux for 3 h and then cooled to room temperature and worked up by the procedure described in 5.2.24.A to yield the *N*-alkylphosphinanilide.

The analogous solid:liquid two-phase alkylation at the more acidic NH position of the diphenylphosphinic hydrazides (Table 5.27) proceeds smoothly in the presence of tetra-*n*-butylammonium hydrogen sulphate [54]. No reaction occurs under the standard liquid:liquid conditions. Hydrolysis of the *N*-alkylated phosphinic hydrazides in refluxing dilute hydrochloric acid provides a convenient and efficient route to *N*-alkylhydrazines [54]. The reaction has been extended to the preparation of *N,N'*-dialkylhydrazines from diphenylphosphinic hydrazide by acylation of the

TABLE 5.27
N-Alkylation of diphenylphosphinic
 hydrazide ($\text{Ph}_2\text{PONHNH}_2$)

Haloalkane	% yield
MeBr	27 ^a
EtBr	96
<i>n</i> -PrBr	93
<i>iso</i> -PrBr	46 ^b
<i>n</i> -BuBr	91
<i>iso</i> -BuBr	87
<i>sec</i> -BuBr	42 ^c
$\text{CH}_2=\text{CHCH}_2\text{Br}$	88
$\text{CH}\equiv\text{CCH}_2\text{Br}$	61
PhCH_2Br	94

^a Carried out in refluxing PhCl, 56% starting material recovered. ^b Using 0.035 mol of catalyst, 40% starting material recovered. ^c Using 0.035 mol of catalyst, 35% starting material recovered.

initially formed *N*-alkylation product, followed by further alkylation and hydrolysis [55].

5.2.25 Alkylation of diphenylphosphinic hydrazide

The bromoalkane (22 mmol) is added dropwise over 1–2 h to $\text{Ph}_2\text{PONHNH}_2$ (4.65 g, 20 mmol), powdered NaOH (3.2 g), K_2CO_3 (4.1 g), and TBA- HSO_4 (1.7 g, 2 mmol) in refluxing PhH (60 ml). The mixture is refluxed for 5 h and then cooled to room temperature and filtered. The solid residue is dissolved in H_2O (50 ml) and the aqueous solution is extracted with CH_2Cl_2 (3×30 ml). The combined organic solutions are dried (MgSO_4) and evaporated to yield the *N*-alkyldiphenylphosphinic hydrazide.

Diethyl *N*-alkylphosphoramides, obtained by the Atherton–Todd procedure (see procedure 5.1.13) are *N*-alkylated under strongly basic two-phase conditions at reflux temperatures [56]. The procedure is obviously limited to alkali-stable reagents and a better route involves the initial formation of the *N*-sodio salt of the phosphoramidate, followed by alkylation under essentially neutral conditions (Table 5.28) [57].

5.2.26 Synthesis of diethyl *N,N*-dialkylphosphoramidates

Method A: The diethyl *N*-alkylphosphoramidate (50 mmol), an excess of the haloalkane (75–100 mmol), TBA- HSO_4 (0.85 g, 2.5 mmol) in PhMe (30 ml) and aqueous NaOH (50%, 25 ml) are stirred vigorously under reflux for 4 h. The mixture is cooled to room temperature and PhMe (50 ml) is added. The dialkylated products are isolated using the procedure described in 5.2.24.A.

Method B: The diethyl *N*-alkylphosphoramidate (20 mmol) in PhH (20 ml) is added

TABLE 5.28
N-Alkylation of diethyl *N*-alkylphosphoramidate

(EtO) ₂ PONHR	Haloalkane	Method (mol of RBr)	% yield	
R = Et	MeI	5.2.26.B (0.1 mol)	85	
	EtBr	5.2.26.B (0.1 mol)	85	
	<i>n</i> -PrBr	5.2.26.B (75 mmol)	67	
	<i>n</i> -BuBr	5.2.26.B (75 mmol)	70	
	CH ₂ =CHCH ₂ Br	5.2.26.B (75 mmol)	93	
<i>n</i> -Pr	CH ₂ =CHCH ₂ Br	5.2.26.A (25 mmol)	86	
	CH≡CCH ₂ Br	5.2.26.B (25 mmol)	88	
	<i>n</i> -Bu	<i>n</i> -PrBr	5.2.26.A (30 mol)	78
PhCH ₂	BrCH ₂ CO ₂ Et	5.2.26.A (22 mmol)	90	
	EtBr	5.2.26.A (30 mmol)	79	
	<i>n</i> -BuBr	5.2.26.B (75 mmol)	98	
	BrCH ₂ CO ₂ Et	5.2.26.A (22 mmol)	88	
	CH ₂ =CHCH ₂ Br	5.2.26.B (75 mmol)	85	
cyclo-C ₆ H ₁₁	CH≡CCH ₂ Br	5.2.26.A (25 mmol)	78	
	EtBr	5.2.26.B (0.1 mol) ^a	67	
	<i>n</i> -BuBr	5.2.26.B (75 mmol) ^a	35	
	Ph	EtBr	5.2.26.B (0.1 mol)	97
	<i>n</i> -BuBr	5.2.26.A (22 mmol)	62	
	<i>n</i> -BuBr	5.2.26.B (75 mmol)	98	
	BrCH ₂ CO ₂ Et	5.2.26.A (22 mmol)	86	

^a 6 h reaction time using 1.9 g (5 mmol) of catalyst.

dropwise over a period of 15 min to NaH (0.53 g) in PhH (15 ml) at 15–20°C. After the evolution of H₂ ceases, an excess of the bromoalkane and TBA-Br (0.32 g, 1 mmol) are added and the mixture is refluxed for 2 h. The mixture is then cooled to room temperature and PhH (50 ml) is added. The product is isolated using the procedure described in 5.2.24.A.

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5.3 ALKYLATION AND ACYLATION OF HETEROARENES [1]

The greater acidities of the heteroaromatic azoles (pK_a ca. 15), compared with simple acyclic and non-aromatic cyclic amines, is reflected in the ease with which the systems are *N*-alkylated and *N*-acylated.

Phase-transfer catalysed alkylation of pyrroles, indoles, and carbazoles has been accomplished in high yield (80–90%) under liquid:liquid two-phase conditions using aqueous sodium hydroxide with benzene [2, 3] or dichloromethane [4–6] as the organic solvent, or in the complete absence of an added solvent [7, 8], and also under solid:liquid two-phase conditions [9, 10]. The *N*-ethylation of indole has been achieved (98%) at room temperature under solid:liquid conditions using diethyl sulphate and potassium hydroxide dispersed on alumina over a 10 minute reaction time [9]. The additional presence of the alumina totally inhibits the solid:liquid two-phase alkylation of indole by iodoethane and, in general, the presence of the alumina is not necessary for high yields of the 1-alkylindoles. The reaction times for solid:liquid alkylation of the azoles [e.g. 11] can be reduced by the use of ultrasound [12] or microwave irradiation [13, 14].

It can be assumed that the azoles are deprotonated by the ‘interfacial exchange’ mechanism, but it is noteworthy that it has been suggested that the rate of alkylation of indole under liquid:liquid two-phase conditions decreases with an increase in the concentration of the sodium hydroxide [8]. The choice of catalyst appears to have little effect on the reaction rate or on the overall yields of alkylated azole. Benzyltriethylammonium chloride, Aliquat, and tetra-*n*-butylammonium hydrogen sulphate or bromide have all been used at *ca.* 1–10% molar equivalents (relative to the concentration of the azole) for alkylation reactions, but *N*-arylation of indole with an activated aryl halide requires a stoichiometric amount of the catalyst [8].

Pyrrole is generally alkylated under basic conditions at the 1-position, but 2- and 3-alkylated products may also be produced [15]. *N*-Alkylation has been optimized using solid:liquid two-phase conditions catalysed by tetra-*n*-butylammonium hydrogen sulphate. Under such conditions in the absence of solvent, iodoalkanes can be used, although their use is precluded under normal liquid:liquid conditions because of the lipophilicity of quaternary ammonium iodides produced during the reaction [16]. The kinetics of such reactions have been reported [17]. Similarly, the ambient anion of indole is susceptible to alkylation at both the 1- and the 3-position [15], but simple primary haloalkanes produce 1-alkylindoles exclusively under liquid:liquid phase-transfer catalysed conditions. However, reactions with benzyl halides and, more particularly, with allyl halides yield significant amounts of the 3-mono- and 1,3-dialkylated indoles [7, 8] (Table 5.29). 1-Alkylated derivatives are preferentially or exclusively produced under solid:liquid two-phase conditions [7, 9]. The choice of catalyst and solvent, and the concentration of the base upon the kinetics and mode of the alkylation of the indole system has been studied [18].

5.3.1 Alkylation of pyrroles, indoles and carbazoles under liquid:liquid two-phase conditions with an added organic solvent

Method A: Aqueous NaOH (50%, 5 ml) and TBA- HSO_4 or TBA-Br (5 mmol) are added to the azole (10 mmol) and the alkylating agent (0.15 mol) in PhH (10 ml). The mixture is stirred at 33°C until the azole is no longer detectable by GLC or TLC analysis (6–22 h). H_2O (10 ml) is added and the organic phase is separated, washed with dilute

TABLE 5.29
Selected examples of the *N*-alkylation of indole

Alkylating agent	Method	% yield
MeI	5.3.1.A	93
Me ₂ SO ₄	5.3.1.A	98
Et ₂ SO ₄	5.3.1.A	95
	5.3.3.A	98
EtBr	5.3.1.B ^a	87
	5.3.2	99
Etl	5.3.1.A	89
<i>n</i> -BuBr	5.3.1.B ^a	88.5
<i>sec</i> -BuBr	5.3.2	10 ^b
<i>iso</i> -C ₅ H ₁₁ Br	5.3.2	93 ^b
<i>n</i> -C ₅ H ₁₁ Br	5.3.1.A	78
CH ₂ Cl ₂	5.3.1.B	43
PhCH ₂ Cl	5.3.1.B ^a	47 ^c
PhCH ₂ Br	5.3.2	93 ^d
CH ₂ =CHCH ₂ Br	5.3.2	39 ^e
Me ₂ C=CHCH ₂ Br	5.3.2	64 ^f
CH≡CCH ₂ Br	5.3.2 ^h	93 ⁱ

^a Using TEBA-Cl. ^b + trace of 1,3-disubstituted indole. ^c + 1,3-disubstituted indole (15%). ^d + 1,3-disubstituted indole (5%). ^e + 3-isomer (15%) and 1,3-disubstituted indole (22%). ^f 1-allylindole (87%) and 1,3-diallylindole (9%) obtained, when a stoichiometric amount of catalyst is used. ^g + 3-isomer (10%) and 1,3-disubstituted indole (21%). ^h at 20°C. ⁱ + allene derivative (2%).

HCl (2M, 15 ml) and H₂O (15 ml), dried (MgSO₄), and evaporated under reduced pressure to give the *N*-alkylazole.

Method B: Aqueous NaOH (50%, 5 ml) is added with stirring to the azole (10 mmol), the alkylating agent (11 mmol) and TBA-Br (0.32 g, 1 mmol) in CH₂Cl₂ (10 ml). The mixture is stirred under reflux for *ca.* 20 h (*ca.* 5 h in the case of azoles substituted with electron-withdrawing groups). The mixture is poured into H₂O (50 ml) and extracted with CH₂Cl₂ (3 × 50 ml). The organic extracts are washed with dilute HCl (2M, 25 ml), brine (25 ml), dried (MgSO₄), and evaporated under reduced pressure to yield the *N*-alkylazole. Omission of the alkylating agent and prolonged reaction time (90 h at 40°C) produces the *N,N'*-diazolymethane.

5.3.2 Alkylation of pyrroles, indoles and carbazoles under liquid:liquid two-phase conditions in the absence of an organic solvent

The alkylating agent (12 mmol) is added to a stirred two-phase system of the azole (10 mmol) and Aliquat (0.45 g, 1 mmol) in aqueous NaOH (50%, 25 ml). The exothermic reaction is stirred at 50–60°C for 1 h (*ca.* 5–6 h for less-reactive higher molecular-weight haloalkanes). The reaction mixture is cooled to room temperature and PhH (50 ml) is added. The organic phase is separated, washed with dilute HCl (2M, 25 ml) and brine (25 ml), dried (MgSO₄), and fractionally distilled to give the *N*-alkylazole.

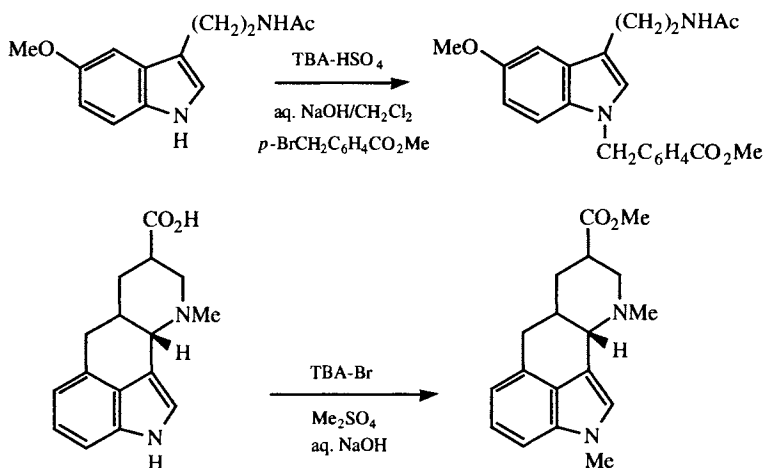
5.3.3 Alkylation of pyrroles, indoles and carbazoles under solid:liquid two-phase conditions

Method A: The azole (10 mmol) is added to powdered KOH (1.6 g, 28 mmol) and TBA-Br, or TBA-HSO₄, (0.25 mmol) and the mixture is stirred at room temperature for 10 min. The alkylating agent (11 mmol) is then added and the mixture is stirred at room temperature for 10–15 min (for the more reactive haloalkanes) or at 50°C for 2 h (for the less reactive haloalkanes). Et₂O (30 ml) is added and the mixture is filtered. Evaporation of the ethereal solution under reduced pressure yields the *N*-alkylazole.

Method B: The azole (10 mmol) and alkylating agent (11 mmol) is added to K₂CO₃ (1.6 g) and TBA-Br (0.3 g, 1 mmol) in MeCOEt (25 ml) and the mixture is stirred at 60°C for *ca.* 12 h. The cooled mixture is evaporated and H₂O (25 ml) and Et₂O (25 ml) are added to the residue. The ethereal solution is separated, dried (Na₂SO₄), and evaporated to yield the *N*-alkylated azole.

Method C (under microwave irradiation): The azole (5 mmol), haloalkane (7.5 mmol), TBA-Br (0.16 g, 0.5 mmol) and K₂CO₃ (2.8 g) are subjected to microwave irradiation (450 W) in a large volume tall beaker for 4–10 min. The alkylated product is isolated as described in 5.3.3.B.

The difference in the acidities of the indolyl NH group and the amidic NH groups allows for selective benzylation at the 1-position of *N*-acetyltryptamines (Scheme 5.14) [19] whereas, when dihydrolysergic acid is *N*-methylated under catalytic conditions [20], it undergoes concomitant conversion into the methyl ester (Scheme 5.14).



Scheme 5.14

A range of alkylating agents have been used for the preparation of 1-alkylpyrroles (Table 5.30). However, in contrast with the corresponding reaction of the indoles, no alkylation of the ring carbon atoms occurs with saturated haloalkanes, but there is

TABLE 5.30
Selected examples of the *N*-alkylation of pyrrole

Alkylating agent	Method	% yield ^a
MeI	5.3.1.B	30
Me ₂ SO ₄	5.3.1.B	68
<i>p</i> -MeOSO ₂ C ₆ H ₄ Me	5.3.1.B	72
EtI	5.3.1.B	28
EtBr	5.3.1.B	84
<i>n</i> -PrBr	5.3.1.B	70
<i>n</i> -BuI	5.3.1.B	33
<i>n</i> -BuBr	5.3.1.B	84
<i>n</i> -BuCl	5.3.1.B	25
<i>n</i> -C ₇ H ₁₁ Br	5.3.1.B	81
<i>n</i> -C ₆ H ₁₃ Br	5.3.1.B	70
<i>iso</i> -PrBr	5.3.1.B	5
CH≡CCH ₂ Br	5.3.1.B	20 ^b
ClCH ₂ CH ₂ CN	5.3.1.B	71
PhCH ₂ Br	5.3.1.B	67
CH ₂ Cl ₂	5.3.1.B ^c	20

^a 20 h at 40°C, ^b + 1-pyrrol-1-ylallene (46%), ^c 90 h at 40°C

evidence that pyrrole reacts with allyl halides to form 1- and 2-allylpyrroles in a ratio of 1:4. This is in accord with previously noted reactions of allyl halides with the 'softer' carbon atom of the pyrrole anion [21]. Prolonged reaction of pyrrole with dichloromethane leads to 1,1'-dipyrrolylmethane [4]. The presence of electron-withdrawing substituents on the pyrrole ring increases the acidity of the pyrrolyl NH group and leads to high yields of the 1-alkylpyrroles under relatively mild conditions (Table 5.31) [5, 22].

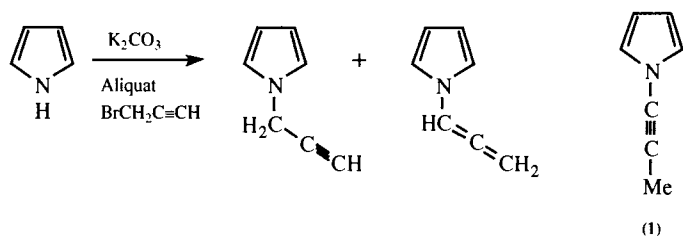
The solid:liquid phase-transfer catalysed reaction of pyrrole with prop-2-ynyl bromide, in the presence of Aliquat, yields 1-(prop-2-ynyl)pyrrole (20%), together

TABLE 5.31
Selected examples of the *N*-alkylation of substituted pyrroles

Pyrrole	Alkylating agent	Method	Reaction times ^a	% yield
2-Me	Me ₂ SO ₄	5.3.1.B	20 h	25
2-CHO	Me ₂ SO ₄	5.3.1.B	20 h	77
2-CHO	CH ₂ Cl ₂	5.3.1.B	5 h	98
2-Ac	Me ₂ SO ₄	5.3.1.B	20 h	94
3-Ac	EtBr	5.3.3.B	12 h	81
	PhCH ₂ Br	5.3.3.B	12 h	65
2-CN	Me ₂ SO ₄	5.3.1.B	20 h	76
2-SMe	CH ₂ Cl ₂	5.3.1.B	5 h	50
^b	CH ₂ Cl ₂	5.3.1.B	4 h	86

^a The reported reaction times of 20 h could be excessive and good yields could probably be obtained after ca. 5 h. ^b 4,5,6,7-tetrahydroindole.

with the isomeric pyrrol-1-ylallene (46%) (Scheme 5.15); 1-(prop-1-ynyl)pyrrole (1) is not observed. Addition of 'basic' alumina to the reaction system inhibits the isomerism of the prop-2-ynyl group [23].



Scheme 5.15

Carbazole [7, 24] has been alkylated under phase-transfer conditions analogous to those used for indoles and pyrroles.

N-Aminoethylazoles, which are frequently encountered as intermediates in the preparation of pharmacologically active compounds, are readily obtained by solid:liquid phase-transfer catalysed reaction of the azole, diazole or triazole and their benzo derivatives with 2-chloroethylammonium chloride at reflux temperature using a procedure analogous to 5.3.3 [25].

Despite the greater acidities of the diazoles and triazoles ($\text{pK}_a = 10\text{--}14$), fairly vigorous reaction conditions are still required for the alkylation of the unsubstituted systems [26] (Table 5.32) and the effectiveness of the alkylation of pyrazoles and imidazoles is enhanced under solid:liquid conditions [27–30]. Under these conditions, quaternization is avoided if no solvent is added [27].

As with the reaction of pyrroles, diazoles and triazoles react with propargyl bromide to yield *N*-substituted products and, depending upon the base strength, either *N*-prop-2-ynylazoles or allenic derivatives are formed [30]. Generally, with potassium carbonate under solid:liquid two-phase conditions at room temperature in the absence of a solvent, the prop-2-ynyl compounds are formed as sole products, whereas with solid potassium hydroxide at elevated temperatures the allenes are obtained as the major products. Benztriazole produces a mixture of the N^1 - and N^2 -prop-2-ynyl, and N^2 -allenic derivatives, whereas with potassium hydroxide only the N^1 -allenic derivative is obtained. The alkynes readily isomerize to the allenes in the presence of base and the quaternary ammonium salt, or upon treatment with methanolic sodium hydroxide. A series of 1-(alk-2-ynyl)imidazoles have been prepared, as intermediates in the synthesis of imidazopyridines [31] and the reaction of 3-hydroxymethylpyrazoles with propargyl bromide leads to pyrazolooxazines [32].

Similarly, the diazoles react with allyl bromide to produce allyl or prop-1-enyl derivatives. The reaction is not particularly base-sensitive, but it is temperature sensitive and the rearranged products are only produced when the reaction is conducted at $>80^\circ\text{C}$ [30].

Nitroimidazoles are *N*-alkylated under solid:liquid conditions [28] or via the

TABLE 5.32
 Selected examples of the alkylation of diazoles and triazoles

Alkylating agent	Method	% yield
<i>Pyrazole</i>		
<i>n</i> -BuBr	5.3.4.A ^a	71
<i>n</i> -C ₁₂ H ₂₅ Br	5.3.4.A ^a	4
PhCH ₂ Cl	5.3.4.C	80
Ph ₂ CHCl	5.3.4.C	70
Ph ₃ CCl	5.3.4.E	55
cyclo-C ₃ H ₇ Br	5.3.4.A ^a	25
CH ₂ Cl ₂	5.3.4.A ^b	93
CH ₂ =CHCH ₂ Br	5.3.4.D ^c	83 ^d
	5.3.4.D ^e	65 ^f
HC≡CCH ₂ Br	5.3.4.D ^e	67 ^h
	5.3.4.D ⁱ	37 ^j
<i>Imidazole</i>		
<i>n</i> -BuBr	5.3.4.A ^a	71
<i>n</i> -C ₈ H ₁₇ Br	5.3.4.A ^a	5
PhCH ₂ Cl	5.3.4.C ^r	76
Ph ₂ CHCl	5.3.4.C	66
Ph ₃ CCl	5.3.4.E	80
PhCH ₂ CH ₂ Br	5.3.4.A ^a	ca. 60
HC≡CCH ₂ Br	5.3.4.D ^k	74 ^h
	5.3.4.D ^j	81 ^j
CH ₂ Cl ₂	5.3.4.A ^b	73
<i>1,2,4-Triazole</i>		
<i>n</i> -BuBr	5.3.4.D	83 ^l
<i>n</i> -C ₈ H ₁₇ Br	5.3.4.D	84 ^m
PhCH ₂ Cl	5.3.4.C	88 ⁿ
Ph ₂ CHCl	5.3.4.C	34 ^o
Ph ₃ CCl	5.3.4.E	57 ^p
CH ₂ =CHCH ₂ Br	5.3.4.D ^r	53 ^q
	5.3.4.D ^e	44 ^r
HC≡CCH ₂ Br	5.3.4.D ^s	47 ^s
	5.3.4.D ^r	^t
CH ₂ Cl ₂	5.3.4.A ^b	65 ^u
CH ₂ Br ₂	5.3.5	77 ^u
<i>Benzimidazole</i>		
CH≡CCH ₂ Br	5.3.4.B	81 ^h
CH ₂ Cl ₂	5.3.4.A ^b	89
<i>2-Methylbenzimidazole</i>		
CH≡CCH ₂ Br	5.3.4.B	45 ^{h,v}
CH ₂ Cl ₂	5.3.4.A ^b	94
<i>Benztriazole</i> (see also Table 5.33)		
CH ₂ =CHCH ₂ Br	5.3.4.D ^s	85 ^w
	5.3.4.D ^r	87 ^v
HC≡CCH ₂ Br	5.3.4.D ^s	77 ^z
	5.3.4.D ^{aa}	30 ^y

^a aq. NaOH/PhH with 4% TBA-Br. ^b aq. NaOH/CH₂Cl₂ with 5% TBA-HSO₄. ^c with KOH (20 mmol) and RX (10 mmol) at room temperature over 48 h. ^d *N*-allyl derivative. ^e With KOH (20 mmol) and RX (10 mmol) at 80 °C over 24 h. ^f *N*-prop-1-enyl derivative. ^g With K₂CO₃ (20 mmol) and RX (15 mmol) at room temperature. ^h *N*-propargyl derivative. ⁱ With KOH (20 mmol) at 40 °C. ^j *N*-azolylallene. ^k With KOH/TiO₂ (10 mmol) at 55 °C. ^l 92 : 8 ratio of 1-:4-isomer. ^m 93 : 7 ratio of 1-:4-isomer. ⁿ 85 : 15 ratio of 1-:4-isomer. ^o 70 : 30 ratio of 1-:4-isomer. ^p 100% 1-isomer. ^q *N*¹-allyl derivative + *N*⁴-allyl (4.5%) derivative. ^r *N*¹-prop-1-enyl derivative. ^s *N*¹-propargyl derivative. ^t Unstable *N*-azolylallene formed. ^u bis-1,2,4,-triazol-1-ylmethane. ^v Addition of alumina increases yield (81%) and totally inhibits isomerism. ^w *N*¹-allyl (61%) + *N*²-allyl (24%) derivatives. ^x With K₂CO₃ (20 mmol) and RX (10 mmol) at 80 °C for 24 h. ^y *N*¹-prop-1-enyl (75%) and *N*²-prop-1-enyl (12%) derivatives. ^z *N*¹-propargyl (63%), *N*²-propargyl (11%) and *N*²-allene (3%) derivatives. ^{aa} With KOH (20 mmol) and RX (20 mmol) at room temperature.

initial isolation of their tetra-*n*-butylammonium salts. Both procedures have several advantages over liquid:liquid two-phase conditions where yields can be low [33].

Optimum conditions for *N*-alkylation of pyrazoles have been investigated [34] and, where isomeric products are possible, alkyl substituents have little effect on the ratio of the alkylated products. Thus, 3(5)-methylpyrazole yields 1,3- and 1,5-dimethylpyrazole in almost equal amounts [35, 36]. Similarly, 3(5)-methylpyrazole reacts with dichloromethane to produce the three possible isomeric di(methylpyrazole-1-yl)methanes in an overall yield of 96% in an almost statistical ratio of the 3,3'- (27%), 3,5'- (50%), and 5,5'-dimethyl derivatives (32%) [37], whereas indazole produces the 1,2'-, 1,2'', and 2,2'-bisindazolylmethanes in a ratio of *ca.* 5:4:1, indicating the greater reactivity of the 1-indazolyl anion [37].

Predictably, 1,2,4-triazole is alkylated preferentially at the 1-position [36, 38, 39]. Specific alkylation at the 4-position can be achieved by the initial reaction with dibromomethane to form the bis-triazol-1-ylmethane (see below), followed by quaternization of the triazole system at the 4-position and subsequent C-N cleavage of the 1,1'-methylenebistriazolium salts [40]. 1,2,3-Benztriazole yields a mixture of the isomeric 1- and 2-alkylated derivatives [41]. The 1-isomer predominates, but the ratio depends on whether the reactions are conducted in the presence, or absence, of a non-polar organic solvent (Table 5.33). Higher ratios of the 1-isomer are obtained under solid:liquid two-phase conditions. Thus, alkylation of 1,2,3-benztriazole with benzyl chloride produces an overall yield of 95% with the 1-:2-isomer ratio of *ca.* 5.7:1; similar reactions with diphenylmethyl and triphenylmethyl chlorides gives overall yields of 95% (9:1 ratio) and 70% (100% 1-isomer), respectively [38]. 6-Substituted purines are alkylated at the N⁹-atom and reaction with 1-bromo-3-chloropropane yields exclusively the 9-chloropropyl derivative (*cf.* reaction with phenols) [42].

5.3.4 *N*-Alkylation of diazoles and triazoles

Method A: The heterocycle (10 mmol) and TBA-Br or TBA-HSO₄ (4 mmol) are added to aqueous NaOH (50%, 10 ml), followed by the alkylating agent (10 mmol) in PhH or CH₂Cl₂ (50 ml). The mixture is stirred for 4–8 h under reflux and then cooled to room temperature. The organic phase is separated, washed with H₂O (3 × 25 ml), dried (Na₂SO₄), and evaporated under reduced pressure to give the alkylated compound.

TABLE 5.33

Selected examples of the alkylation of benztriazoles under liquid:liquid two-phase conditions

Haloalkane	Method 5.3.6.A		Method 5.3.6.B	
	Ratio of 1-:2-isomer	Overall % yield	Ratio of 1-:2-isomer	Overall % yield
MeI	3.1:1	79	2.4:1	91
EtBr	1.4:1	89	1.2:1	86
<i>n</i> -PrBr	1.8:1	85	1.2:1	90
<i>n</i> -BuBr	1.6:1	88	1.1:1	80
PhCH ₂ Br	4.5:1	98	1.9:1	94

Method B: The heterocycle (8.5 mmol), K_2CO_3 (1.2 g), powdered KOH (0.6 g) and TEBA-Cl or Aliquat (0.18 g, *ca.* 0.4 mmol) in CH_2Cl_2 (25 ml) are stirred under reflux for 6–8 h. The cooled mixture is filtered and the solid residue is extracted with hot CH_2Cl_2 (2×100 ml). The combined organic solutions are evaporated to yield the *N*-alkyl derivative.

Method C: The alkylating agent (30 mmol) is added to the heterocycle (30 mmol), K_2CO_3 (4.1 g), powdered KOH (1.68 g) and TBA-Br (0.48 g, 1.5 mmol) in xylene or MeCN (200 ml) and the mixture is heated under reflux for 14–20 h. The solids are removed by filtration and washed with xylene or MeCN (3×10 ml). The combined organic solutions are concentrated and chromatographed on silica to yield the *N*-alkylated derivative.

Method D: The azole (10 mmol), powdered KOH or K_2CO_3 (10–20 mmol) and TBA-Br (0.16 g, 0.5 mmol) are mixed under ultrasound for 15 min. The haloalkane (10–20 mmol) is added and the mixture is stirred until TLC analysis indicates completion of the reaction. The mixture is extracted with CH_2Cl_2 (2×25 ml) and the extracts are evaporated to yield the *N*-alkylated product, which is purified by chromatography.

Method E: The heterocycle (30 mmol) is added to Na (0.69 g, 30 mmol) in refluxing xylene (200 ml) and the mixture is refluxed for 15 h. TBA-Br (0.48 g, 1.5 mmol) is added with the alkylating agent (30 mmol) and the mixture is refluxed for a further 8 h. The *N*-alkylated product is isolated by the procedure described in 5.3.4.C.

5.3.5 Specific synthesis of 4-alkyl-1,2,4-triazoles

1,2,4-Triazole (1.38 g, 20 mmol), powdered KOH (2.24 g), and TBA-Br (0.19 g, 0.6 mmol) in H_2O (0.15 ml) are stirred at room temperature for 1 h. CH_2Br_2 (5.22 g, 30 mmol) is added and stirring is continued for a further 48 h. The mixture is extracted with CH_2Cl_2 (5×20 ml) and chromatographed on silica, using EtOAc as the eluent, to give bis(1,2,4-triazol-1-yl)methane, which is converted into the 4,4'-dialkylated 1,1'-methylenebis(1,2,4-triazolium) salt with an excess of the appropriate alkylating agent. The salt is deprotected by refluxing in *n*-BuOH for 5–10 h. Evaporation of the solvent yields the 4-alkyl-1,2,4-triazole (refluxing EtOH cleaves the methylene bridge, but the reaction time is extended to 5 days).

5.3.6 Alkylation of benztriazole

Method A in the presence of a non-polar organic solvent: Aqueous KOH (or NaOH) (18 M, 45 ml) is added to 1,2,3-benztriazole (17.85 g, 0.15 mol), the haloalkane (0.18 mol), and TEBA-Cl (6.8 g, 30 mmol) in PhH (300 ml), and the two-phase system is stirred under reflux for 2 h. The mixture is then cooled and the organic phase is separated, dried (Na_2SO_4), and fractionally distilled to give the *N*-alkylated product.

Method B in the absence of an organic solvent: The haloalkane (0.18 mol) is added to 1,2,3-benztriazole (17.85 g, 0.15 mol) and TEBA-Cl (6.8 g, 30 mmol) in aqueous KOH or NaOH (50%, 375 ml) and the mixture is stirred at room temperature for 4 h. The organic layer is separated and the aqueous phase is extracted with PhH (2×50 ml). The organic solutions are dried (Na_2SO_4) and fractionally distilled to give the *N*-alkylated product.

The reaction of dichloromethane with equimolar amounts of pyrazole and imidazole under liquid:liquid two-phase catalytic conditions yields the three possible

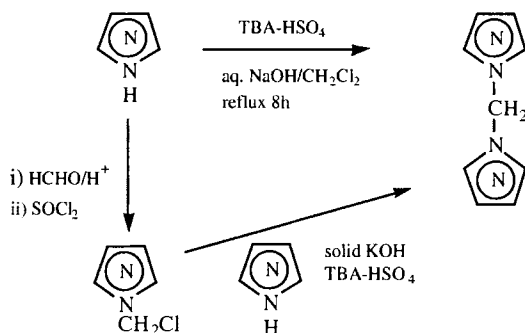
TABLE 5.34

Synthesis of unsymmetrical bis(diazolyl)methanes, $Az^1CH_2Az^2$, from the diazole, Az^1H , and the *N*-chloromethyldiazole, Az^2CH_2Cl

Az^1H	Az^2	% yield
Imidazole	1-Pyrazolyl	65
3,5-Dimethylpyrazole	1-Pyrazolyl	55
3,5-Dimethylpyrazole	3,5-Dimethyl-1-pyrazolyl	85
Pyrazole	3,5-Dimethyl-1-pyrazolyl	65
4-Methyl-3(5)-phenylpyrazole	3,5-Dimethyl-1-pyrazolyl	<i>a</i>
2-Methylbenzimidazole	2-Methyl-1-benzimidazolyl	95

a 28% 4-methyl-5-phenyl derivative and 35% 4-methyl-3-phenyl derivative.

products in almost the expected ratio, i.e. 32% bispyrazol-1-ylmethane, 49% 1-(pyrazol-1-ylmethyl)imidazole, and 19% bis(imidazol-1-yl)methane [36] and, from a solid:liquid two-phase system, the ratio is 28 : 50 : 22. The slightly higher yields of the bispyrazolyl derivative, compared with the bisimidazolyl compound, reflects the greater reactivity of the pyrazole system [36]. The preparation of unsymmetrical bis(diazolyl)methanes in high yield (Table 5.34) can be controlled by the intermediate formation of the *N*-chloromethyldiazoles (Scheme 5.16) [37]. Benztriazole also reacts with dichloromethane under solid:liquid two-phase conditions to produce the three possible isomeric bis(benztriazolyl)methanes (N^1,N^1 30.4%; N^1,N^2 24.4%; N^2,N^2 5%) and, with chloroform, the N^1,N^1,N^1 -, N^1,N^1,N^2 - and N^1,N^2,N^2 -tris(benztriazolyl)methanes are produced in 20.4%, 9.5% and 1.46% yields, respectively [43].



Scheme 5.16

5.3.7 Controlled synthesis of bis(diazolyl)methanes

Powdered KOH (1.68 g, 30 mmol) and anhydrous K_2CO_3 (1.38 g, 10 mmol) are added to the 1-chloromethyldiazolium chloride (10 mmol), the diazole (10 mmol) and TBA- HSO_4 (0.17 g, 0.5 mmol) in PhH (50 ml). The mixture is stirred under reflux for 8 h and then

maintained at room temperature for 16 h. The solid is separated by filtration, washed with boiling PhH (2 × 25 ml), and the combined PhH solutions are evaporated under reduced pressure to yield the bis(diazolyl)methane.

Dibenz[*b,f*]azepine and 1,4-dihydropyridine are *N*-alkylated (40–100%) with a range of alkylating agents under standard liquid:liquid two-phase conditions [44, 45].

The two-phase alkylation reactions have been extended to the acylation of simple heteroaromatic systems. Generally, the required conditions are milder than those employed for the alkylation reactions, but an excess of the acylating agent is usually required, owing to its facile hydrolysis in the basic media. Thus, benzimidazole and its 2-alkyl and 2-aryl derivatives have been benzoylated [46], and pyrrole and indole have been converted into a range of *N*-acyl [47, 48] and *N*-sulphonyl derivatives [48–53] (Table 5.35 and Table 5.36).

N-Sulphonylation of pyrroles and indoles, using a liquid:liquid two-phase procedure [3, 48, 50–54], is superior to the traditional methods, which frequently require preformation of the heteroaryl sodium derivative, whereas *N*-sulphonylation of indole using a sulphonyl chloride in the presence of pyridine leads to the formation of the 1,4-dihydro-4-indol-3-ylpyridine [49]. The liquid:liquid two-phase procedure outlined below is suitable for most *N*-sulphonylation reactions with heteroaromatic compounds, but it is sometimes advisable to add a second quantity of the sulphonyl chloride during the course of the reaction [22, 47].

TABLE 5.35
Acylation and sulphonylation of indole

Reactive reagent	Method	% yield
MeCOCl	5.3.8.B	88
<i>n</i> -BuCOCl	5.3.8.B	81
<i>t</i> -BuCOCl	5.3.8.B	84
PhCOCl	5.3.8.B	95
ClCO ₂ Et	5.3.8.B	77
ClCONMe ₂	5.3.8.B	94
MeSO ₂ Cl	5.3.9	92
PhSO ₂ Cl	5.3.9	96
3-MeC ₆ H ₄ SO ₂ Cl	5.3.9	94
2,4,6- <i>iso</i> -Pr ₃ C ₆ H ₂ SO ₂ Cl	5.3.9	85

TABLE 5.36
Selected examples of the acylation of substituted indoles

Substituent	Acylating agent	Reaction conditions ^a	% yield of 1-acylindole
3-CHO	(<i>t</i> -BuO) ₂ CO	5.3.8.A (rt. 5 min)	90
	PhSO ₂ Cl	5.3.9 (rt. 30 min) ^a	85
	TosCl	5.3.9 (rt. 30 min) ^a	90

^a Using 30% aqueous NaOH and TBA-I.

5.3.8 *N*-Acylation of indole

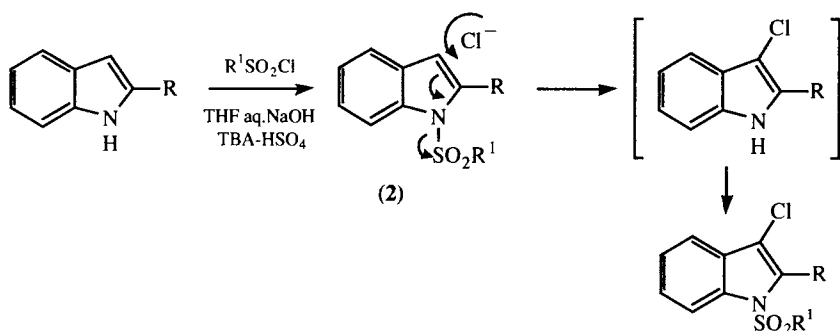
Method A: The indole (13.8 mmol) in PhH (50 ml) is added to aqueous NaOH (30%, 50 ml) TBA-I (0.44 g, 1.38 mmol) and the acylating agent (14.5 mmol), and the mixture is stirred at room temperature. On completion of the reaction, the aqueous phase is separated, extracted with PhH (20 ml), and the combined PhH solutions are dried (Na_2SO_4) and evaporated to yield the 1-acylindole.

Method B: Powdered KOH (1.0 g, 30 mmol) is added with stirring to the indole (1.17 g, 10 mmol) and TBA- HSO_4 (33.9 mg, 0.1 mmol) in CH_2Cl_2 (30 ml). The acyl chloride (15 mmol) in CH_2Cl_2 (10 ml) is added dropwise over 15–20 min and the exothermic reaction is cooled to maintain the temperature at *ca.* 15–20°C. The mixture is stirred for 20 min at room temperature (reaction with *t*-BuCOCl requires 2 h at room temperature and CICONMe₂ requires 2 h at 50°C) and then filtered. The solid is washed with CH_2Cl_2 (25 ml) and the combined organic solutions are dried (Na_2SO_4) and evaporated to yield the *N*-acylindole.

5.3.9 *N*-Sulphonylation of pyrroles and indoles

Aqueous NaOH (50%, 10 ml) is added with stirring to the pyrrole or indole (10 mmol) and TBA-Br or TBA- HSO_4 (1 mmol) in PhH or CH_2Cl_2 (30 ml). After 5 min, the sulphonyl chloride (15 mmol) in PhH or CH_2Cl_2 (15 ml) is added dropwise over a period of 20 min at room temperature and the mixture is stirred for a further period at room temperature. When TLC analysis shows the completion of the reaction (*ca.* 30 min; 2,4,6-tris-*iso*-propylbenzenesulphonyl chloride requires 150 min at 50°C), the organic phase is separated, washed with H_2O (3×20 ml), and filtered through silica using PhH as the eluent. Addition of *n*- C_6H_{14} precipitates the ammonium catalyst and the decanted solution is evaporated under reduced pressure to give the *N*-sulphonylindole.

It is interesting that an attempted *N*-benzenesulphonylation of 2-arylindoles in tetrahydrofuran, using tetra-*n*-butylammonium hydroxide and aqueous sodium hydroxide, leads to the 3-chloro-1-benzenesulphonyl derivative (Scheme 5.17; **2**, $\text{R} = \text{Ar}$, $\text{R}' = \text{Ph}$), as a minor product, as well as the required *N*-sulphonylindole (**2**, $\text{R} = \text{Ar}$, $\text{R}' = \text{Ph}$) [55]. The reaction presumably proceeds via a nucleophilic attack by the chloride anion at the 3-position of (**2**), with concomitant loss of the benzenesulphonyl group, followed by a prototropic shift and subsequent sulphonylation of the 1*H*-indole. Although this mechanism is reasonable, the addition of a large excess of sodium bromide does not produce the corresponding 3-bromoindole, which is formed when benzenesulphonyl bromide is used.



Scheme 5.17

Similar side reactions were observed with 2-methylindole and arenesulphonyl chlorides, but the reaction of 2-substituted indoles with methanesulphonyl chloride gave the expected 1,2-disubstituted indoles (**2**, $R^1 = \text{Me}$).

It has been reported that the reaction of 2-(2-pyridyl)indole with benzenesulphonyl chloride, under phase-transfer catalytic conditions, yields three products, which have been recorded as being the 3-, 4- and 6-benzenesulphonylindoles [56], or 3-chloro-1-benzenesulphonyl-2-(2-pyridyl)indole, as the major product, with the 1-benzenesulphonyl- and 1,3-bis(benzenesulphonyl) derivatives, as the minor products [55]. In the light of the earlier discussion, the latter structural assignments appear to be more likely to be correct.

Alkylation of potentially tautomeric heteroaromatic systems under basic phase-transfer catalytic conditions normally occurs on the 'softer' heteroatom [*cf.* 57]. Thus, although 2- and 4-pyridones are alkylated on the annular nitrogen atom and the exocyclic oxygen atom, *N*-alkylation of the 2-pyridones predominates to the extent of *ca.* 5 : 1 (or greater under solid:liquid reaction conditions [58]), whereas the relative predominance of *N*-alkylation of the 4-isomer is only *ca.* 3 : 1 [59] (Table 5.37 and 5.38). These ratios are comparable with those obtained for the base-catalysed alkylation of the pyridones by traditional methods and, not unexpectedly, *S*-alkylation of the corresponding pyridithiones occurs to the total exclusion of *N*-alkylation [60]. Catalysed solid:liquid acylation has also been reported [58].

TABLE 5.37
Alkylation of 2- and 4-pyridones and pyridithiones

Haloalkane	% overall yield	Ratio of <i>N</i> -alkylation to <i>O</i> -(or <i>S</i> -) alkylation
<i>2-Pyridone</i>		
<i>iso</i> -PrBr	34	3.0 : 1
<i>n</i> -BuBr	80	5.6 : 1
PhCH ₂ Cl	60	5.2 : 1
CH ₂ =CHCH ₂ Br	75	5.2 : 1
<i>4-Pyridone</i>		
<i>iso</i> -PrBr	58	1.9 : 1
<i>n</i> -BuBr	72	2.3 : 1
CH ₂ =CHCH ₂ Br	44	2.3 : 1
<i>2-Pyridithione</i>		
MeI	78	100% <i>S</i> -alkylation
EtBr	78	100% <i>S</i> -alkylation
<i>iso</i> -PrBr	70	100% <i>S</i> -alkylation
<i>n</i> -BuBr	81	100% <i>S</i> -alkylation
PhCH ₂ Cl	70	100% <i>S</i> -alkylation
<i>4-Pyridithione</i>		
MeI	95	100% <i>S</i> -alkylation
EtBr	82	100% <i>S</i> -alkylation
<i>iso</i> -PrBr	72	100% <i>S</i> -alkylation
<i>n</i> -BuBr	80	100% <i>S</i> -alkylation
PhCH ₂ Cl	75	100% <i>S</i> -alkylation
CH ₂ =CHCH ₂ Br	85	100% <i>S</i> -alkylation

TABLE 5.38
 Alkylation of acridones

Haloalkane	% overall yield	Ratio of <i>N</i> - to <i>O</i> -alkylation
Mel	45	100% <i>N</i> -alkylation
EtBr	45 ^a	4.0 : 1
<i>n</i> -PrBr	43 ^a	1.9 : 1
<i>n</i> -BuBr	65 ^a	3.0 : 1
<i>n</i> -C ₅ H ₁₁ Br	55	2.3 : 1
<i>n</i> -C ₆ H ₁₃ Br	55	2.3 : 1
<i>n</i> -C ₇ H ₁₅ Br	41	3.0 : 1
<i>n</i> -C ₈ H ₁₇ Br	46	1.9 : 1
<i>n</i> -C ₉ H ₁₉ Br	42	3.0 : 1
<i>n</i> -C ₁₀ H ₂₁ Br	47	5.6 : 1
<i>n</i> -C ₁₁ H ₂₃ Br	45	1.9 : 1
<i>n</i> -C ₁₂ H ₂₅ Br	48	3.0 : 1
PhO(CH ₂) ₃ Br	61	2.3 : 1
Et ₃ N ⁺ (CH ₂) ₃ Cl	66	5.6 : 1
Et ₃ N ⁺ (CH ₂) ₂ Br	43	4.0 : 1
PhCH ₂ Cl	63 ^a	3.0 : 1
CH≡CCH ₂ Br	95 ^b	100% <i>N</i> -alkylation

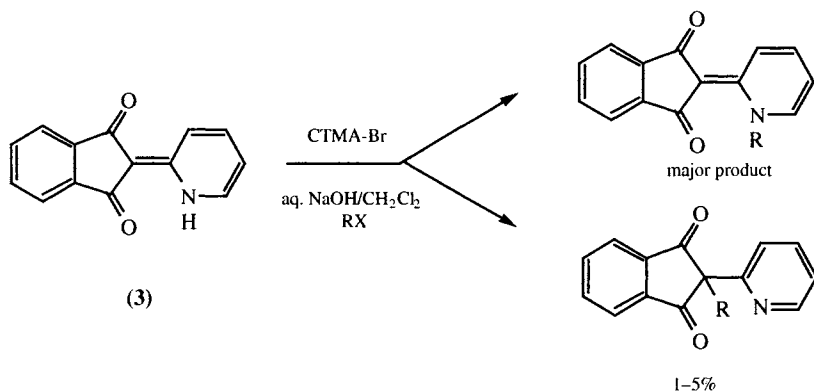
^a Higher yields of *N*-alkylated derivatives (>75%) have been reported for reactions in aq. NaOH–MeCOEt, with TEBA–Cl. ^b Liquid:liquid two-phase system at 20 °C using Aliquat.

5.3.10 Liquid:liquid two-phase alkylation of pyridones and related systems

The alkylating agent (20 mmol) in PhH (or PhMe) (30 ml) is added with stirring to the tautomeric system (10 mmol) and TBA–Br (1.95 g, 6 mmol) in aqueous NaOH (50%, 3 ml). The mixture is stirred at 60 °C for 6 h. The organic layer is then separated, washed with H₂O until the washings are neutral, dried (Na₂SO₄), and filtered through silica. Evaporation of the filtrate gives the alkylated product. Work-up of the alkylated acridone by stirring the crude product with dilute HCl (6M, 20 ml) at room temperature for 8 h, followed by extraction with PhH (3 × 50 ml), gives the *N*-alkylated compound; the alkyl ether is destroyed under the acidic conditions [61].

The presence of substituents on the pyridine ring, which reduce the basicity of the annular nitrogen atom, not only shifts the pyridone-hydroxypyridine equilibrium towards the hydroxy form [62], but they also inhibit *N*-alkylation. Thus, for example, 3,5,6-trichloro-2-hydroxypyridine is alkylated preferentially on the oxygen atom. Predictably, alkylation of 3-hydroxypyridine and of 2-amino-3-hydroxypyridine leads to the 3-alkoxypyridines in high yield under basic conditions [63] (see Chapter 3).

Alkylation of the 2-(1,2-dihydropyrid-2-yl)indane-1,3-diones (**3**) (Scheme 5.18) by traditional methods, using sodium hydride in apolar or dipolar solvents, leads to a mixture of the C²- and *N*-alkylated derivatives in moderate to low yield (Scheme 5.18). In contrast, two-phase alkylation results in almost complete regioselective *N*-alkylation in high yield [64].



Scheme 5.18

Alkylation of a series of 4-quinolones under basic two-phase conditions yields a mixture of the *O*- and *N*-alkylated derivatives [65]. The ratio of the two isomers depends on the substituents. *N*-Alkylation is predominant (*N*:*O* ratio = *ca.* >4:1) for most compounds but, somewhat surprisingly, the presence of a methyl group at either the 2- or 8-position results in a higher, or sometimes exclusive, yield of the *N*-alkylated product, irrespective of other substituents on the system.

Although it was originally claimed [66] that the base-catalysed two-phase methylation of acridone produced the methyl ether to the exclusion of *N*-methylation, it is evident that this was probably an incorrect structural assignment. Not surprisingly, it has been established unequivocally that predominant alkylation of acridone with a range of reagents occurs at the annular nitrogen atom [24] and that variations in the reported *O*:*N* alkylation ratios probably result from any alkyl ethers, that are formed, being destroyed by an acidic work-up [61] or undergoing rearrangement to the thermodynamically more stable *N*-alkyl compounds. In the case of the reaction with dimethyl sulphate or iodomethane, it has been proposed that *N*-methylation is the predominant reaction pathway [24, 61]. However, as indicated in Chapter 1, the use of iodoalkanes is not to be recommended, as the reaction rate and the yields for the alkylation are considerably lower than they are for bromoalkanes. The procedure has been put to good use in the synthesis of acronycine [67]. Thioacridones are alkylated and acylated exclusively on the sulphur atom [68] (see 4.1.4.D).

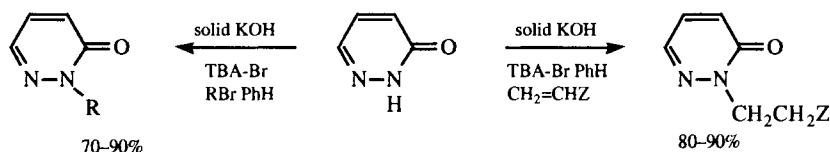
It has been reported that alkylation of 2-pyridone and 2-quinolone and other related potentially tautomeric azinones under solid-liquid phase-transfer catalytic conditions generally produces the *N*-alkylated derivatives exclusively in 65–90% yield [58], although it has been suggested that the yield of the *O*-alkylated derivative can be increased by the use of long-chain quaternary ammonium salts and when bulky alkylating agents are used [69].

Alkylation of 9-aminoacridine, under conditions analogous to those used for acridone, provides a convenient route to the 9-alkylaminoacridines [70], which are

normally obtained by a laborious route via the unstable 9-chloroacridines. Compared with acridone, the rate of alkylation of the amino group is slow even with simple primary haloalkanes (see Section 5.1) unless a high concentration of the catalyst is used, and the low yields (40–45%) are only acceptable in view of the ease of the reaction. Under certain conditions, *N*-alkylation of the ring has also been observed [70] and minor amounts (<20%) of the 10-alkylacridonimines are formed; the two isomers can be separated via their hydrochloride salts by fractional crystallization. These results should be compared with the normal alkylation of the potentially tautomeric amino heteroaromatic systems under neutral conditions, which leads exclusively to alkylation of the annular nitrogen atom [62]. It is noteworthy that, in the reaction with (2-chloroethyl)diethylamine, the 10-diethylaminoethyl compound was the only product reportedly isolated.

Reaction of 9-aminoacridine with the highly reactive benzyl chloride results in the formation of the bis-benzylated derivative. Caution should be exercised in the use of large quantities of benzyltriethylammonium chloride when a poor alkylating agent is being used, as it can lead to the formation of the 10-benzyl derivatives of the 9-alkylaminoacridines through reaction with the catalyst [71]. This problem can be obviated by using tetra-*n*-butylammonium salts or Aliquat.

2*H*-Pyridazin-3-ones behave in a manner analogous to that shown by the pyridones under basic two-phase conditions to produce the *N*-alkylated derivatives with primary and secondary haloalkanes and with acrylonitrile or ethyl acrylate [72] (Scheme 5.19). Alkylation of pyridazinones, by classical methods, generally requires strongly basic conditions, high temperatures, and long reaction times. The milder phase-transfer catalysed procedure permits alkylation of systems which have base-sensitive groups. 6-Substituted 2*H*-pyridazin-3-ones react with a range of alkylating agents (Table 5.39).



Scheme 5.19

The procedure has been used for the synthesis of potential anti-ulcer agents [Scheme 5.19, $R = (CH_2)_nNH_2$] via the phthalimido derivative, and $R = (CH_2)_nCSNR_2$ via the cyano derivatives [73, 74].

5.3.11 Solid:liquid two-phase *N*-alkylation of 2*H*-pyridazin-3-ones

Method A: The haloalkane (20 mmol) and TBA-Br (0.56 g, 2 mmol) in PhH (200 ml) is added to the 2*H*-pyridazin-3-one (10 mmol) and powdered KOH (0.56 g, 10 mmol), and the mixture is stirred at room temperature for 5–6 h. The organic phase is separated,

TABLE 5.39
Selected *N*-alkylation of 6-substituted 2*H*-pyridazin-3-ones

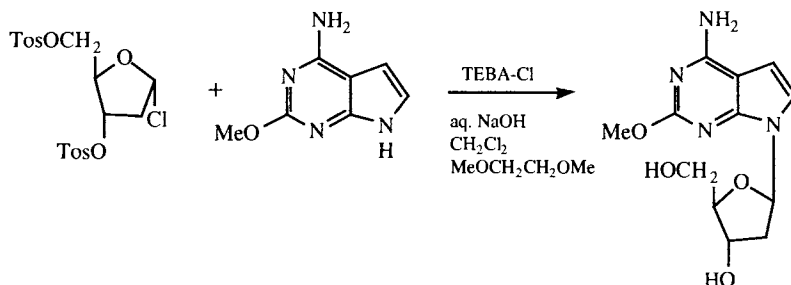
6-Substituent	Alkylating agent	Method	% yield 2-alkylated derivative
Me	<i>n</i> -BuBr	5.3.11.A (5 h)	79
CO ₂ Et	<i>n</i> -BuBr	5.3.11.A (6 h)	81
CONMe ₂	<i>n</i> -BuBr	5.3.11.A (6 h)	46
NMe ₂	<i>n</i> -BuBr	5.3.11.A (6 h)	88
Ph	<i>iso</i> -BuBr	5.3.11.A (6 h)	65
Ph	<i>sec</i> -BuBr	5.3.11.A (6 h)	80
Ph	<i>n</i> -C ₈ H ₁₇ Br	5.3.11.A (6 h)	83
Ph	PhCH ₂ Br	5.3.11.A (8 h)	89
Ph	Ph(CH ₂) ₂ Br	5.3.11.A (8 h)	92
Ph	NC(CH ₂) _n Br	5.3.11.A (6 h)	80–86 (<i>n</i> =3–5)
Ph	Br(CH ₂) _n Br ^a	5.3.11.A (6 h)	69–85 (<i>n</i> =2–5)
Ph	BrCH ₂ CO ₂ Et	5.3.11.A (8 h)	81
Ph	CH ₂ =CHCH ₂ Br	5.3.11.A (6 h)	82
Me	CH ₂ =CHCN	5.3.11.B (5 h)	88
Ph	CH ₂ =CHCN	5.3.11.B (8 h)	95
Ph	CH ₂ =CHCO ₂ Et	5.3.11.B (8 h)	86

^a Using three equivalents of alkylating agent.

washed with aqueous HCl (10%, 180 ml) and H₂O (200 ml), dried (Na₂SO₄), and evaporated under reduced pressure to yield the *N*-alkylated pyridazinone.

Method B: The α,β -unsaturated nitrile or ester (30 mmol) in PhH (100 ml) is added to the 2*H*-pyridazin-3-one (15 mmol), TBA-Br (0.97 g, 3 mmol) and powdered KOH (0.84 g, 15 mmol). The mixture is stirred at room temperature for 5–8 h and the product is isolated as described in 5.3.11.A.

Potentially tautomeric pyrimidines and purines are *N*-alkylated under two-phase conditions, using tetra-*n*-butylammonium bromide or Aliquat as the catalyst [75–77]. Alkylation of, for example, uracil, thiamine, and cytosine yield the 1-mono- and 1,3-dialkylated derivatives [77–81]. Theobromine and other xanthines are alkylated at N¹ and/or at N³, but adenine is preferentially alkylated at N⁹ (70–80%), with smaller amounts of the N³-alkylated derivative (20–25%), under the basic two-phase conditions [76]. These observations should be compared with the preferential alkylation at N³ under neutral conditions. The procedure is of importance in the derivatization of nucleic acids and it has been developed for the *N*-alkylation of nucleosides and nucleotides using haloalkanes or trialkyl phosphates in the presence of tetra-*n*-butylammonium fluoride [80]. Under analogous conditions, pyrimidine nucleosides are *O*-acylated [79]. The catalysed alkylation reactions have been extended to the glycosidation of pyrrolo[2,3-*d*]pyrimidines, pyrrolo[3,2-*c*]pyridines, and pyrazolo[3,4-*d*]pyrimidines (e.g. Scheme 5.20) [e.g. 82–88] as a route to potentially biologically active azapurine analogues.



Scheme 5.20

5.3.12 *N*-Alkylation of nucleosides and nucleotides

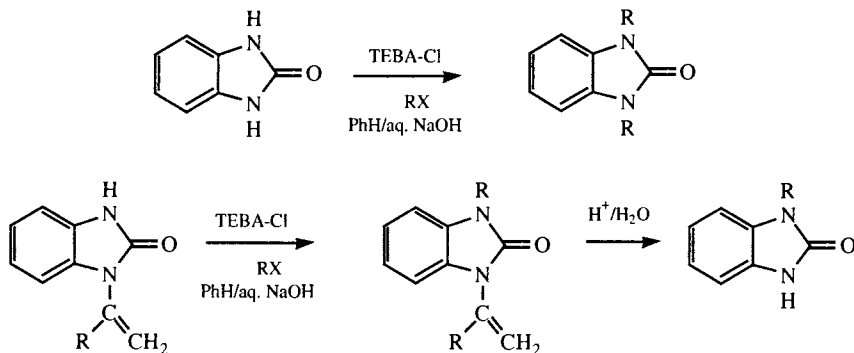
The haloalkane or trialkyl phosphate (3 mmol) is added to the nucleoside or nucleotide (0.01 mmol) and TBA-F (1.2 mg, 0.005 mmol) in dry THF (10 ml) and the mixture is stirred at room temperature for 1 h. The alkylated product can be isolated by chromatography on silica.

5.3.13 Glycosidation of purines, pyrimidines and related compounds

The heterocycle (3 mmol) and TEBA-Cl (50 mg, 0.22 mol) in CH_2Cl_2 :1,2-MeO(CH_2)₂OMe (20:1 v/v, 20 ml) are added to aqueous NaOH (50%, 20 ml) and the mixture is stirred for 1 min. The halogenose (3 mmol) in CH_2Cl_2 (5 ml) is then added and the mixture is stirred for a further 45 min. The organic phase is separated and the aqueous phase is extracted with CH_2Cl_2 (2 \times 25 ml). The combined organic solutions are washed with H_2O (25 ml), dried (MgSO_4), and evaporated under reduced pressure to yield the product.

Heterocycles having highly acidic NH sites, e.g. phthalimide, 2-pyridone, imidazole, react with ethylene carbonate under conditions analogous to those employed for the synthesis of β -hydroxyethyl esters (3.3.1.E) to give the *N*- β -hydroxyethyl heterocycles [89].

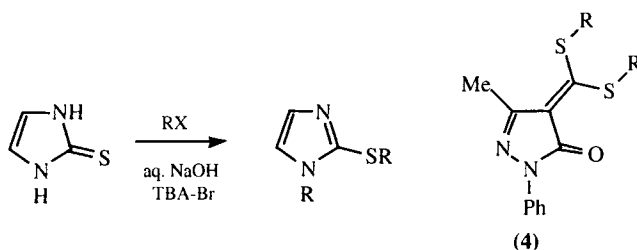
In accord with the ‘hard–soft acid–base’ theory, it is not unexpected that benzimidazol-2-ones are alkylated on both the N¹- and N³ atoms under mildly basic liquid:liquid two-phase conditions [90]. *N*-Alkylation of 1-isopropenylbenzimidazol-2-ones, followed by treatment with acid, provides a viable route to mono-alkylated derivatives (Scheme 5.21).



Scheme 5.21

In contrast, but again not unexpectedly, imidazole-2-thione is dialkylated on the sulphur atom and at the 1-N position (Scheme 5.22). Even with equimolar amounts of the heterocycle and the alkylating agent, only the dialkylated derivative is isolated [91].

The catalysed alkylation of 1*H*,4*H*-pyrazol-5-ones is solvent dependent. In benzene, bis-alkylation occurs at the 4-position whereas, in a carbon disulphide:benzene mixture, *O*-alkylation is observed, although the major product (4, Scheme 5.22) results from nucleophilic attack by the pyrazolone on the carbon disulphide, followed by alkylation of the dithiolate dianion [92]. The catalysed reaction of 2-thiono-3-arylthiazolidin-4-ones with alkylating agents under solid:liquid two-phase conditions results in alkylation at the 5-position (60–80%) [93]. The aldol condensation of the thiazolidinones with aryl aldehydes is also catalysed by quaternary ammonium salts.



Scheme 5.22

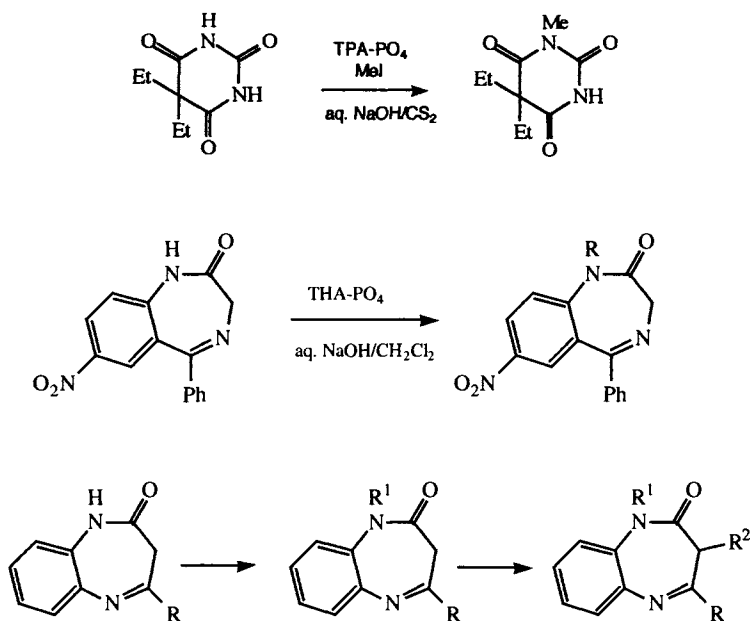
5.3.14 C-Alkylation of 2-thiono-3-arylthiazolidin-4-ones

The alkylating agent, or aryl aldehyde, (30 mmol) is added to the thiazolidinone (30 mmol), K_2CO_3 (6.9 g), and TBA-Br (10 mg, 0.3 mmol) in PhH or dioxan (70 ml) and the mixture is stirred at *ca.* 33°C for 1–8 h until the reaction is shown to be complete by TLC analysis. The mixture is filtered, evaporated, and the residue is washed well with H_2O and taken up in Et_2O . Evaporation of the ethereal solution yields the 5-alkylated product (e.g. R = Me, 81%, Et, 77%; CH_2CHO , 64%, COMe, 61%, CO_2Et , 76%).

Barbiturates [94, 95] and diazapirones [96–99] are alkylated (e.g. Scheme 5.23) and arylated (see Chapter 2.2) on the ‘amidic’ nitrogen atom under liquid:liquid phase-transfer catalytic conditions and the procedure has been used as pretreatment of the non-volatile heterocycles for GLC analysis.

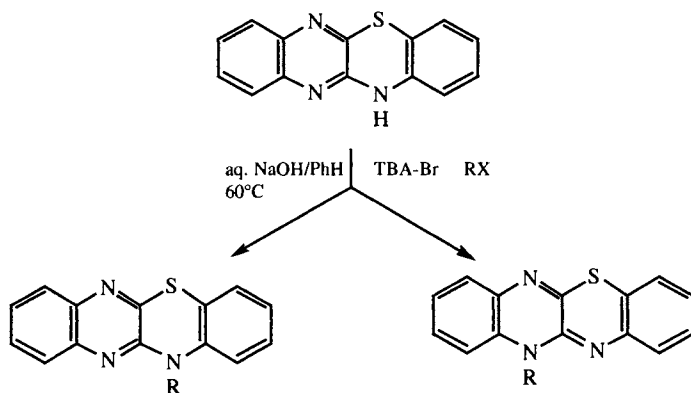
5.3.15 General procedure for alkylation of ‘amidic’ and ‘thioamidic’ heterocyclic systems

The haloalkane (60 mmol for monoalkylation) is added with stirring to the heterocycle (50 mmol)* and TBA-Br or TEBA-Cl (5 mmol) in PhH or CH_2Cl_2 (50 ml) and aqueous NaOH (50%, 20 ml). The mixture is stirred at 60°C for *ca.* 4–5 h and then cooled to room temperature. The organic phase is separated, washed with H_2O (2×25 ml), dried ($MgSO_4$), and evaporated to yield the *N*-alkylated product. (* The preformed sodium salts of the barbiturates have been used in the absence of a solvent or aqueous NaOH.)



Scheme 5.23

The potentially tautomeric 12*H*-quinoxalino[2,3-*b*]benzo-1,4-thiazines are alkylated at either the 11- or 12-positions [100] in a *ca.* 3:7 ratio (Scheme 5.24) under liquid:liquid two-phase conditions, analogous to those employed for the alkylation of 'amidic' heterocycles.



Scheme 5.24

Reissert compounds (>70%), derived from benzimidazole, phthalazine, quinoline and isoquinoline, have been prepared by a simple catalysed one-pot *N*-acylation of the appropriate heterocycle, followed by reaction with cyanide ion [e.g. 101–103].

5.3.16 Reissert compounds

The acylating agent (0.7 mmol) is added dropwise to the heteroarene (7 mmol), KCN (0.45 g) and TBA-Br* (0.23 g, 0.7 mmol) in CH_2Cl_2 (25 ml) over 10 min with constant stirring. The mixture is refluxed for 2.5 h, cooled to room temperature, and the organic phase is separated. The organic solution is washed sequentially with H_2O , aqueous HCl (0.1 M), H_2O , and aqueous NaOH (0.1 M) until the washings are neutral, dried (MgSO_4), and evaporated to yield the Reissert compound. (*Longer reaction times are required when TEBA-Cl is used.)

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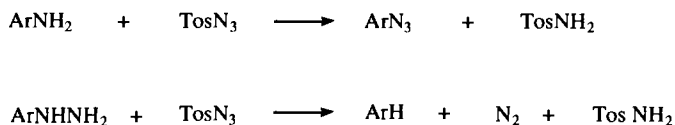
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5.4 MISCELLANEOUS REACTIONS

Arylamines and hydrazines react with tosyl azide under basic conditions to yield aryl azides [1] and arenes [2], respectively, by an aza-transfer process (Scheme 5.25). Traditionally, the reaction of anilines with tosyl azides requires strong bases, such as alkyl lithiums, but acceptable yields (>50%) have been obtained under liquid:liquid phase-transfer catalytic conditions. Not surprisingly, the best yields are obtained when the aryl ring is substituted by an electron-withdrawing substituent, and the yields for the corresponding reaction with aliphatic amines are generally poor (~20%). Comparison of the catalytic effect of various quaternary ammonium salts showed that tetra-*n*-butylammonium bromide produces the best conversion, but differences between the various catalysts were minimal [1].

Yields of the arenes from the hydrazines are variable and generally low (<40%) for simple aryl compounds, although acceptable yields (50–90%) are obtained for the π -electron-deficient heteroaryl derivatives. In this respect, the procedure has some utility, as the more usual reductive conversion of haloheteroarenes into the parent



Scheme 5.25

compounds frequently results in partial hydrogenation of the heteroaromatic system. Tetraethylammonium chloride has been used as the phase-transfer catalyst of choice, but with the exception of the poor efficiency of tetra-*n*-butylammonium bromide, there is little difference between the more commonly used catalysts [2].

Although aliphatic azides can be prepared under liquid:liquid phase-transfer catalytic conditions [3–5], they are best obtained directly by the reaction of a haloalkane with sodium azide in the absence of a solvent [e.g. 6, 7]. Iodides and bromides react more readily than chlorides; cyclohexyl halides tend to produce cyclohexene as a by-product. Acetonitrile and dichloromethane are the most frequently used solvents, but it should be noted that prolonged contact (>2 weeks) of the azide ion with dichloromethane can produce highly explosive products [8, 9]; dibromomethane produces the explosive bisazidomethane in 60% yield after 16 days [8].

Direct conversion of α -bromo esters into amino esters by hydride reduction of the azido ester (without isolation) produces yields in excess of 80% [7]. However, bromomalonates fail to form the azido ester under similar conditions. Instead, oxidative dimerization occurs to yield the ethene-1,1,2,2-tetracarboxylate (see Section 6.1) [10].

Aryloxysulphonyl azides are obtained in good yield from the reaction of the sulphonyl chloride with tetra-*n*-butylammonium azide [11].

3-Bromo-3-phenyldiazirine reacts with a 6-fold excess of tetra-*n*-butylammonium azide to yield benzonitrile in a 90% yield [12]. It is assumed that the nitrile originates from the spontaneous loss of nitrogen from the intermediate 3-azido compound; the corresponding reaction with the chlorodiazirine is slower. Preformed tetra-*n*-butylammonium azide as well as polymer-supported quaternary ammonium azides, have been used for the conversion of acid chlorides into acyl azides (see 9.3.3) [13,14]. Glycosyl azides are produced in an analogous manner from glycosyl bromides [15].

5.4.1 Conversion of arylhydrazines into arenes

TosN₃ (0.37 g, 2 mmol), the arylhydrazine (2 mmol), and TEA-Br (0.1 g, 0.5 mmol) in xylene (10 ml) are added to aqueous NaOH (50%, 10 ml) and the mixture is refluxed until the azide has been fully consumed (2–10 h). The organic phase is separated and the aqueous phase is extracted with PhH (3 × 10 ml). The combined organic solutions are dried (MgSO₄) and evaporated to yield the arene [e.g. PhH 40% (6 h); pyridine 98% (6 h) from 2-hydrazino derivative; pyridazine 79% (8 h) from 3-hydrazino derivative)].

5.4.2 Aliphatic azides (CAUTION : A highly explosive azide may be formed when dichloromethane is used as the solvent)

Method A: The haloalkane (80 mmol) is added to aqueous NaN_3 (25%, 12 ml) and Aliquat (1.62 g, 4 mmol) and the mixture is stirred under reflux until GLC analysis shows the reaction to be complete. The organic phase is separated, dried (MgSO_4), and fractionally distilled to yield the azide [e.g. *n*-alkyl (C4–10) 89–93%].

Method B: Amberlite IR-400 (Cl⁻ form) is shaken repeatedly with aqueous NaN_3 (20%), washed with H_2O , MeOH and Et_2O , and dried under vacuum. The haloalkane (1 mol) in CH_2Cl_2 or MeCN (4 ml) is added to the resin (4.9 g, equivalent to 12.5 mol of azide) and the mixture is shaken for 1–2 h. The resin is removed by filtration, washed with CH_2Cl_2 (10 ml), and the combined organic solutions are evaporated to yield the alkyl azide (>95%).

5.4.3 Glycosyl azides

The peracetylglycosyl bromide (10 mmol) in CH_2Cl_2 (40 ml) is stirred vigorously at room temperature with TBA- HSO_4 (3.39 g, 10 mmol) and NaN_3 (2.6 g) in aqueous NaHCO_3 (40 ml) for 1–2 h. When the reaction is complete, as shown by TLC, the organic phase is separated, washed well with aqueous NaHCO_3 , H_2O and brine, dried (Na_2SO_4), and evaporated to yield the glycosyl azide (93–98%).

Vinyl azides have been prepared via the reaction of sodium azide with 1-(*N*-acetyl-*N*-nitrosoamino)alkan-2-ols [16]. The reaction proceeds via the initial formation of the carbene (see Section 7.1).

5.4.4 Vinyl azides

The 1-(*N*-acetyl-*N*-nitrosoamino)alkan-2-ol (12.5 mmol) in *n*- C_5H_{12} (15 ml) is added to NaN_3 (10 g), NaOH (1 g) and Aliquat (0.75 g, 1.9 mmol) in H_2O (10 ml) at ca. 5°C. The organic phase is separated and subjected to chromatography on alumina to yield the azide [e.g. 1-(*N*-acetyl-*N*-nitrosoaminomethyl)cyclohexan-1-ol yields azidomethylenecyclohexane, 56%].

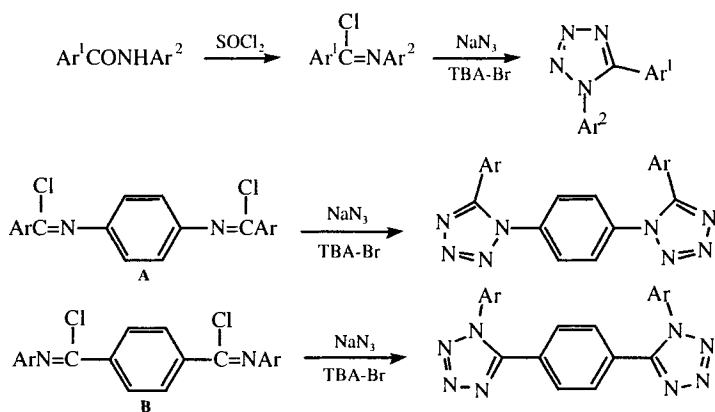
A single report of the addition of sodium azide to cyclohexene in the presence of iodine under phase-transfer catalytic conditions to produce 2-iodocyclohexanyl azide has the potential for extension to other alkenes [17]. The analogous reaction of cyclohexene with potassium thiocyanate and iodine produces 2-iodocyclohexyl isothiocyanate (17%) and 2-iodocyclohexanyl thiocyanate (61%). Similar products are obtained with other alkenes [17].

5.4.5 2-Iodocyclohexanyl azide

NaN_3 (0.41 g, 6.25 mmol) in H_2O (1.5 ml) is added to I_2 (0.76 g, 3 mmol) and Adogen (30 mg, 0.06 mmol) in CHCl_3 (10 ml). Cyclo- C_6H_{10} (0.1 g, 1.25 mmol) is added dropwise and the mixture is stirred in the dark at 20°C for 48 h. The organic phase is separated, shaken with aqueous NaHSO_3 (sat. soln., 5 ml), and filtered through silica. Evaporation

of the filtrate gives the iodo azide which, upon chromatography from silica, is separated into the *trans*-(50%) and *cis*-isomer (4%).

The reaction of sodium azide with *N*-aryl chloroimines, obtained from benzanilides and thionyl chloride, to form 1,5-disubstituted tetrazoles is catalysed by tetra-*n*-butylammonium bromide (Scheme 5.26, Table 5.40) [18] in variable yields, but generally <85%. 5-Butyl-2,3-diphenyltetrazolium salts have also been used as catalysts [18, 19]. 1,5-Disubstituted tetrazoles are also obtained from a one-pot sequential reaction of carbodimides with sodium azide and an aroyl chloride in the presence of tetra-*n*-butylammonium chloride [20]. 5-Chlorotetrazoles are obtained from the catalysed reaction of aryldichloroisocyanides with sodium azide (Scheme 5.26) [21].



Scheme 5.26

TABLE 5.40
1,5-Aryl tetrazoles from anilides

Anilide			Anilide		
Ar ¹	Ar ²	% yield of tetrazole	Ar ¹	Ar ²	% yield of tetrazole
Ph	3-O ₂ NC ₆ H ₄	89	3-Pyridyl	Ph	48
3-O ₂ NC ₆ H ₄	Ph	91	4-Pyridyl	Ph	75
4-O ₂ NC ₆ H ₄	4-O ₂ NC ₆ H ₄	91	compound A		71
2-Pyridyl	Ph	36	compound B		57

5.4.6 1,5-Diaryl tetrazoles

The benzanilide (6.1 mmol) and SOCl₂ (3.3 g) are heated at 75–80°C for 1 h and excess SOCl₂ is then evaporated under reduced pressure. The chlorinated product is dissolved in CH₂Cl₂ (10 ml) and NaN₃ (0.52 g, 8 mmol) and TBA-Br (97 mg, 0.3 mmol) in CH₂Cl₂ (10 ml) and H₂O (20 ml) are added at 20–25°C. The mixture is stirred for 1 h and the organic phase is then separated, washed with H₂O (3 × 30 ml), dried (MgSO₄), and evaporated to give the tetrazole.

5.4.7 1-Aryl-5-(*N*-aryl-*N*-aroylamino)tetrazole

The aroyl chloride (10 mmol) in PhMe (10 ml) is added dropwise to the carbodiimide (10 mmol), NaN₃ (975 mg, 15 mmol) and TBA-Cl (0.28 g, 1 mmol) in PhMe (40 ml) at room temperature under N₂. After *ca.* 3–4 h, the mixture is heated to 95 °C for 30 min. The cooled mixture is filtered and evaporated under reduced pressure to yield the tetrazole, which is purified by chromatography from silica [e.g. 64% from PhN=C=NPh and PhCOCl; 55% from TolN=C=NTol and PhCOCl; 70% from PhN=C=NPh and TolCOCl].

5.4.8 1-Aryl-5-chlorotetrazoles

NaN₃ (24.7 g, 0.38 mol) and TBA-Br (5.48 g, 17 mmol) in H₂O (80 ml) are added to the aryl-1,1-dichloroisocyanide (43.5 g, 0.25 mol), obtained from the reaction of Cl₂ with the aryl isothiocyanate, in PhMe (400 ml) and the mixture is stirred at room temperature for *ca.* 1.5 h. The aqueous phase is saturated with NaCl and the organic phase is separated, dried (Na₂SO₄), and evaporated to yield the tetrazole (~100%).

The formation of 3-diazo-3*H*-indoles from the reaction of indoles with tosyl azide is catalysed by the addition of benzyltriethylammonium chloride [22]. In the absence of the catalyst, 3,3'-azoindoles are formed to the complete exclusion of the diazoindoles.

5.4.9 3-Diazo-3*H*-indoles

Aqueous NaOH (40%, 3 ml) is added dropwise to the indole (5.2 mmol), TosN₃ (1.02 g, 5.2 mmol) and TEBA-Cl (30 mg, 0.13 mmol) in PhH (40 ml). The mixture is stirred at room temperature for 18 h in the dark and the organic phase is then separated, washed with H₂O (3 × 30 ml), dried (Na₂SO₄), and evaporated to yield the diazoindole, which can be purified by chromatography from silica [e.g. 3-diazo-2-phenyl-3*H*-indole, 75%; 3-diazo-2-(2-pyridyl)-3*H*-indole, 87%; 3-diazo-2-(2-thienyl)-3*H*-indole, 83%].

The reaction of activated methylene groups with tosyl azide to yield the corresponding diazo derivatives proceeds in high yield [23]. The phase-transfer catalysed reaction is sensitive to the strength of base used; the reaction of acetoacetic esters requires relatively mild conditions, otherwise diazoacetic esters are produced (Table 5.41).

TABLE 5.41
Diazoketones and esters

Methylene compound	Solvent	Catalyst	Product	% yield
PhCH ₂ COMe	PhH	TBA-Br	PhC(N ₂)COMe	100 ^a
MeCOCH ₂ CO ₂ Et	<i>n</i> -C ₅ H ₁₂	TBA-Br	MeCOC(N ₂)CO ₂ Et	90 ^b
	<i>n</i> -C ₅ H ₁₂	TBA-Br	N ₂ CHCO ₂ Et	53
MeCOCH ₂ CO ₂ <i>t</i> -Bu	CH ₂ Cl ₂	Aliquat	MeCOC(N ₂)CO ₂ <i>t</i> -Bu	92 ^c
	<i>n</i> -C ₅ H ₁₂	TBA-Br	N ₂ CHCO ₂ <i>t</i> -Bu	89
CH ₂ (CO ₂ <i>t</i> -Bu) ₂	PhH	Aliquat	N ₂ C(CO ₂ <i>t</i> -Bu) ₂	87 ^a

^a Using 10M NaOH. ^b Using Na₂CO₃ (sat. soln) instead of 3M NaOH. ^c At 0 °C, 77% using Na₂CO₃ (sat. soln) at 25 °C in *n*-C₅H₁₂.

5.4.10 Diazoketones and esters

The activated methylene compound (5 mmol) in PhH or *n*-C₅H₁₂ (40 ml) is stirred at 25°C for 15 h with TosN₃ (0.99 g, 5 mmol), the catalyst (0.1 mmol) and aqueous NaOH (3M, 3 ml). The organic phase is separated, washed well with water, dried (Na₂SO₄), and fractionally distilled under reduced pressure to give the diazo compound. (**CAUTION:** the diazoalkanes are potentially explosive.)

Formazans are conveniently produced under phase-transfer catalytic conditions from *N*-aryl hydrazones and aryl diazonium salts [24]. Yields vary from *ca.* 50% to 70%, but the procedure is superior to the standard synthesis.

5.4.11 Formazans

The arylhydrazone Ar¹NHN=CHAR² (5 mmol), Na₂CO₃·H₂O (3.1 g) and TBA-Br (0.16 g, 0.5 mmol) in CH₂Cl₂ (50 ml) and H₂O (20 ml) are stirred at room temperature for 10 min. The aryl diazonium salt Ar³N₂X (5.75 mmol) in H₂O (30 ml) is added dropwise at 5°C and the mixture is stirred for 1 h. The organic phase is separated, washed with H₂O (2 × 50 ml), dried (Na₂SO₄), and evaporated to yield the formazan Ar¹NHN=C(Ar²)N=NAr³ [e.g. Ar¹, Ar², Ar³: Ph, Ph, Ph, 71%; 4-MeC₆H₄, Ph, Ph, 54%; 4-MeOC₆H₄, Ph, Ph, 54%; 4-O₂NC₆H₄, Ph, Ph, 51%].

N-(*p*-Toluenesulphonyl)sulphilimines have been prepared under solid:liquid phase-transfer catalytic conditions from the reaction of sulphides with Chloramine-T [25] (see Section 4.5). Osmium-catalysed oxyamination of alkenes by Chloramine-T under two-phase conditions is aided by the addition of benzyltriethylammonium chloride. β-Aminoalkanols are obtained in good yields (60–75%) [26].

5.4.12 Oxyamination of alkenes

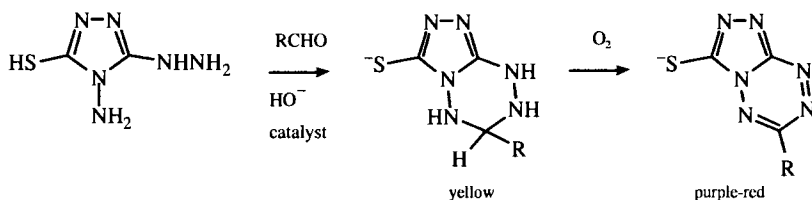
The alkene (1 mmol) in CHCl₃ (5 ml) is stirred at 55–60°C with OsO₄ in *t*-BuOH (0.2 M, 0.5 ml), TosN(Cl)Na·3H₂O (0.35 g, 1.25 mmol) and TEBA-Cl (11.4 mg, 0.05 mmol) in H₂O (5 ml). When the reaction is complete, as shown by TLC analysis, NaHSO₃ (0.11 g) is added and the mixture is refluxed for 3–6 h. The aqueous phase is separated, extracted with CHCl₃ (10 ml), and the combined organic phases are washed well with brine, aqueous NaOH (1%), dried (MgSO₄), and evaporated to yield the 2-(*N*-tosylamino) alcohol [e.g. 62% from C₈H₁₇CH=CH₂; 71% from PhCH=CHPh + 9% amino ketone; 75% from cyclohexene; MeCH(NHTos)CH(OH)CO₂Et (36%) and MeCH(OH)CH(NHTos)CO₂Et, (22%) from MeCH=CHCO₂Et].

Isocyanides and arylamines react with Chloramine-T when catalysed by the addition of benzyltriethylammonium chloride to produce *N*-tosylguanidines in good yield (58–78%) [27]. The reaction is thought to proceed via the initial *N*-chlorination of the arylamine.

5.4.13 *N*-Tosylguanidines

TEBA-Cl (50 mg, 0.2 mmol) is added to a well-stirred suspension of the alkyl isocyanide (10 mmol), the arylamine (10 mmol) and $\text{TosN}(\text{Cl})\text{Na}\cdot 3\text{H}_2\text{O}$ (2.3 g, 10 mmol) in CH_2Cl_2 (50 ml) (**CAUTION**: After an induction period, the reaction may become violent.) After 20 h, H_2O is added and the organic phase is separated, dried (Na_2SO_4), and evaporated to yield the *N*-tosylguanidine.

Qualitative spot tests for aldehydes, in the presence of ketones, are generally only reliable for water-soluble compounds. This problem can be overcome by the use of 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole (Purpald®, Aldrich Chemical Company) in the presence of Aliquat (Scheme 5.27). Under aerial oxidation, the initially formed colourless cyclic adduct changes colour through red to purple. The colourless cyclic aminal can also be formed by ketones, but only the adducts derived from the aldehydes are oxidized to the purple bicyclic aromatic system [28]. Weakly electrophilic aldehydes, e.g., 4-methoxybenzaldehyde, reacts slowly, but will give the positive coloration upon gentle heating to *ca.* 70 °C for one or two minutes.

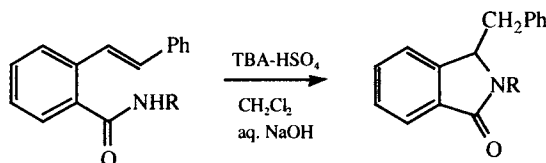


Scheme 5.27

5.4.14 Phase-transfer catalysed colour test for aldehydes

The aldehydic material under test (*ca.* 0.1 ml) is added to Purpald® (50 mg) and Aliquat (0.11 g, 0.25 mmol) in PhMe (5 ml). Aqueous NaOH (10%, 1 ml) is added and the mixture is shaken well. The initial yellow coloration of the organic phase rapidly changes to a deep rust colour to confirm the presence of the aldehyde, but remains yellow for ketones.

2-Carboxamidostilbenes undergo a slow 5-exo-trig ring closure (Scheme 5.28) under basic conditions. No evidence has been found for the alternative 6-endo-trig cyclization and the ease of the reaction is reported to be enhanced by the addition of tetra-*n*-butylammonium hydrogen sulphate [29]. The reaction is only applicable to *N*-alkyl derivatives, but fails with the *N*-*t*-butyl derivative, presumably as a result of steric hindrance. No experimental details have been given for the reaction.



Scheme 5.28

It has been shown that the thermolysis of arenesulphonyl azides with benzene to yield *N*-arenesulphonylazepines (44–80%) is aided by the addition of Adogen [30]. Sulphonylazepines have also been obtained from the reaction of tetra-*n*-butylammonium salts of sulphonamides with benzene in the presence of xenon difluoride; the reaction probably proceeds via the intermediate nitrene [31].

5.4.15 *N*-Sulphonylazepines

Method A: The sulphonyl azide (50 mmol), PhH (200 g), NaHCO₃ (1.68 g) and Adogen (0.22 g, 5 mmol) are heated in an autoclave at 125°C for 3 h. The cooled reaction mixture is filtered, washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the azepine, which is purified by chromatography on alumina.

Method B: The sulphonyl chloride (50 mmol), PhH (200 g), NaN₃ (4 g, 50 mmol), NaHCO₃ (1.68 g) and Adogen (0.22 g, 5 mmol) are heated in an autoclave at 40°C for 3 h and then at 125°C for a further 3 h. The product is isolated as described in 5.4.15.A.

Method C: XeF₂ (0.338 g, 2 mmol) is added portionwise over 1 h to TBA-NHSO₂R (2 mmol) in PhH (5 ml) at 80°C. When the evolution of Xe ceases, the mixture is cooled to room temperature, dried (Na₂SO₄), and evaporated to yield the sulphonylazepine, which is purified by chromatography from silica (e.g. R = Me, 41%; Ph, 47%; 4-MeC₆H₄, 42%).

Alkyl and glycosyl isocyanates and isothiocyanates are produced in good yield under phase-transfer catalytic conditions using either conventional soluble catalysts or polymer-supported catalysts [32, 33]. Acyl isothiocyanates are obtained under similar conditions [34]. *N*-Aryl phosphoramidates are converted via their reaction with carbon disulphide under basic conditions into the corresponding aryl isothiocyanates, when the reaction is catalysed by tetra-*n*-butylammonium bromide [35].

5.4.16 Acyl isothiocyanates

Aqueous KSCN (33%, 33 ml, *ca.* 0.11 mol) is added dropwise over *ca.* 25 min to the acid chloride (43 mmol) and TBA-Br (0.55 g, 1.7 mmol) in PhH (20 ml) and the mixture is stirred at room temperature for *ca.* 2 h. The aqueous phase is separated and extracted with PhH (3 × 5 ml). The dried (MgSO₄) organic solutions are fractionally distilled to yield the acyl isothiocyanate.

5.4.17 Alkyl and aryl isothiocyanates from phosphoramidates

The diethyl *N*-alkyl or *N*-aryl phosphoramidate (40 mmol) in PhH (50 ml) is added dropwise to NaH (1.2 g) and TBA-Br (0.64 g, 2 mmol) in PhH (150 ml) over 30 min at 50°C. When the evolution of H₂ ceases (*ca.* 2 h), the mixture is cooled to room temperature and CS₂ (6.1 g, 80 mmol) is added. The mixture is refluxed for a further 2 h, then allowed to stand at room temperature for *ca.* 12 h, and filtered. The filtrate is evaporated and the residue is extracted with *n*-C₆H₁₄ (2 × 50 ml). The extracts are washed with H₂O (2 × 20 ml), dried (MgSO₄), and fractionally distilled to yield the isothiocyanate. RNCS [e.g. R = *n*-Bu, 91%; cyclo-C₆H₁₁, 84%; cyclo-C₃H₉, 91%; PhCH₂, 76%; Ph, 83%].

Quaternary ammonium salts catalyse the trimerization of arylisocyanates to give isocyanurates [36, 37]. The intermediate diarylbiuret can also be prepared under catalytic conditions.

5.4.18 Aryl isocyanurates

Method A: TBA-F in THF (1M, 0.84 ml, 0.84 mmol) is added to the aryl isocyanate (4.2 mmol) and the mixture is stirred at 70°C. After *ca.* 1 min, the mixture solidifies. After subjecting it to low pressure to evaporate unreacted isocyanate, the solid is taken up in CH₂Cl₂ (25 ml). The solution is washed well with brine, dried (MgSO₄), and evaporated to yield the aryl isocyanurate (e.g. 85% from PhNCO; 65% from 4-MeOCOC₆H₄NCO; 91% from 4-Me₃SiOCOC₆H₄NCO).

Method B: Aliquat (0.1 g, 0.25 mmol), NaCN (50 mg) and the arylisocyanate (10 mmol) are stirred until the mixture solidifies. H₂O (20 ml) is added and the aqueous mixture is filtered to yield the isocyanurate (>90%).

5.4.19 1,5-Diarylbiuret

The arylisocyanate (30 mmol) in PhH (50 ml) is added slowly with stirring over 90 min to KNCO (4.9 g) and TEBA-Cl (4.55 g, 20 mmol) in H₂O (50 ml). The solid biuret is collected and recrystallized from MeOH.

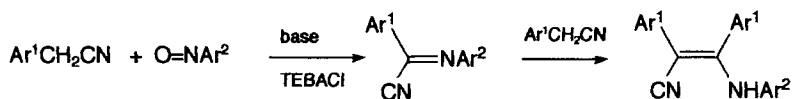
It has been reported that the conversion of carbonyl compounds into their oximes, which is normally acid-catalysed, can be effected under basic conditions in the presence of tetra-*n*-butylammonium chloride [37]. Good yields are generally obtained with most aldehydes and ketones with the exception of benzophenone.

Organoboranes react with ethyl 4-nitrobenzenesulphonyloxycarbamate under basic two-phase conditions in the presence of benzyltriethylammonium chloride or Aliquat to yield ethyl *N*-alkylcarbamates [38]. The reaction probably proceeds via the initial formation of the nitrene, which reacts with the borane to form a B-N⁺ zwitterion. Subsequent rearrangement and solvolysis leads to the product. Aliquat is the better catalyst for the higher-molecular-weight boranes.

5.4.20 Ethyl *N*-alkylcarbamates

The trialkylborane (3 mmol) in CH₂Cl₂ (3 ml) is added to 4-O₂NC₆H₄SO₃NHCO₂Et (0.87 g, 3 mmol) and TEBA-Cl or Aliquat (0.6 mmol) in CH₂Cl₂ (10 ml) at room temperature. Aqueous NaHCO₃ (1 M, 9 ml) is added dropwise and the mixture is stirred for 2 h. H₂O (50 ml) is added and the mixture is extracted with CH₂Cl₂ (3 × 35 ml). The extracts are washed well with brine, dried (MgSO₄), and evaporated to yield the *N*-alkylcarbamate (e.g. *n*-PrNHCO₂Et, 97%; *n*-BuNHCO₂Et, 95%; *n*-C₅H₁₁NHCO₂Et, 76%).

In the nitrogen analogue of the aldol condensation, nitrosoarenes condense with arylacetonitriles to produce cyanoimines [39]. When two equivalents of the acetonitrile is used, further condensation occurs to form β-cyanovinylamines (Scheme 5.29) [40].



Scheme 5.29

5.4.21 Condensation of arylacetonitriles with nitrosoarenes

$\text{Ar}^1\text{CH}_2\text{CN}$ (5 or 10 mmol*) and Ar^2NO (5 mmol) are added to TEBA-Cl (30 mg, 0.16 mmol) in aqueous NaOH (50%, 10 ml) and PhH (10 ml) at 30 °C and the mixture is stirred for 4 h. The mixture is then poured into conc. HCl (15 ml) at 0 °C and the mixture is extracted with PhH (3 × 25 ml). The dried (Na_2SO_4) organic solutions are evaporated to yield the condensation product. (*with 5 mmol, $\text{Ar}^1\text{C}(\text{CN})=\text{NAr}^2$, e.g. $\text{Ar}^1 = \text{Ph}$, $\text{Ar}^2 = \text{Ph}$: 72%; Ph , 4-MeC₆H₄: 61%; 4-MeC₆H₄: 61%; 4-MeC₆H₄, Ph : 63%; with 10 mmol, $\text{Ar}^1\text{C}(\text{CN})=\text{C}(\text{Ar}^1)\text{NHA}^2$, Ph , Ph : 93%; Ph , 4-MeC₆H₄: 86%; 4-MeC₆H₄, Ph : 59%.)

Secondary amines are converted into the corresponding *N*-nitrosoamines in high yield (~90%) by sodium nitrite and *N*-chloro- or *N*-bromosuccinimide under liquid:liquid two-phase conditions in the presence of lipophilic quaternary ammonium salts [41]. There is evidence that nitrosyl chloride is initially formed, which reacts with the nitrite ion to generate N_2O_4 . Hydrophilic ammonium salts do not promote the formation of N_2O_4 and the final products are the *N*-haloamines.

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– 6 –

Formation of C–C Bonds

6.1 INTRODUCTION

The simplest C–C bond formation reaction is the nucleophilic displacement of a halide ion from a haloalkane by the cyanide ion. This was one of the first reactions for which the kinetics under phase-transfer catalysed conditions was investigated and patented [1–3] and is widely used [e.g. 4–12]. The reaction has been the subject of a large number of patents and it is frequently used as a standard reaction for the assessment of the effectiveness of the catalyst. Although the majority of reactions are conducted under liquid:liquid two-phase conditions, it has also been conducted under solid:liquid two-phase conditions [13] but, as with many other reactions carried out under such conditions, a trace of water is necessary for optimum success. Triphase catalysis [14] and use of the preformed quaternary ammonium cyanide [e.g. 15] have also been applied to the conversion of haloalkanes into the corresponding nitriles. Polymer-bound chloroalkanes react with sodium cyanide and cyanoalkanes under phase-transfer catalytic conditions [16].

In a sequential continuous process, alcohols are converted initially into the corresponding chloroalkanes, which are flushed without isolation into an aqueous mixture of sodium cyanide and the quaternary ammonium catalyst to produce nitriles [17].

Attempts to convert 1-bromo-1-phenylacetonitrile into the dicyano derivative under liquid:liquid two-phase conditions have been unsuccessful but, on addition of aqueous sodium hydroxide, 1,2-dicyano-1,2-diphenylethene is formed by an oxidative dimerization mechanism [18]. Similarly, diethyl bromomalonate fails to produce the corresponding azide with lithium azide under catalytic conditions; the sole product (15%) is the ethene-1,1,2,2-tetracarboxylate [19].

Benzylic halides produce isonitriles (80–90%) with tetramethylammonium cyanoargentate, prepared from tetramethylammonium chloride and silver cyanide [20]. The reaction fails with simple haloalkanes.

6.1.1 Alkyl cyanides

Method A. (liquid:liquid conditions): The haloalkane (0.1 mol), or dihaloalkane (0.05 mol), is added to NaCN or KCN (0.12 mol) and the quaternary ammonium catalyst

(12 mmol) in H₂O (40 ml) at room temperature and then stirred at 80–95°C for 1–6 h. The mixture is extracted with CH₂Cl₂ (3 × 30 ml) and the combined organic solutions are washed well with brine, dried (MgSO₄ or CaCl₂), and evaporated. The residue is taken up in Et₂O, filtered, and fractionally distilled to yield the nitrile.

Method B. (solid:liquid conditions): Finely ground KCN (1.95 g, 30 mmol) is shaken with H₂O (0.54 g), the haloalkane (20 mmol), or dihaloalkane (10 mmol), and Aliquat (0.22 g, 0.4 mmol) for 5 min at room temperature. The mixture is stirred for a further period (Table 6.1) and Et₂O (50 ml) is then added. The mixture is filtered through Florosil and evaporated to yield the nitrile (>90%).

Method C. (tri-phase catalysis): NaCN (0.6 g) in H₂O (1 ml) and the haloalkane (0.6 mmol) in PhMe (1 ml) are shaken for 2 min with the quaternary ammonium resin (74 mg), obtained by reaction of Me₂BuN with poly-4-chloromethylstyrene. The mixture is kept at 110°C for *ca.* 5.5 h and it is then filtered and extracted with CH₂Cl₂ (3 × 10 ml). The dried (MgSO₄) extracts are evaporated to yield the nitrile.

Method D from the alcohol: SOCl₂ (32.8 g) in PhMe (155 ml) is added to a stirred solution of the alcohol (0.25 mol) in THF (21 ml) and PhMe (250 ml) at a flow rate of *ca.* 7–10 ml/min. The mixture decants directly at *ca.* 7–10 ml/min into TEBA-Cl (2.85 g, 12.5 mmol) and NaCN (18 g) in H₂O (600 ml) and aqueous NaOH (53%, 57 ml). The organic phase is separated and the nitrile is isolated as described in 6.1.1.A.

Method E (using acetone cyanhydrin): TBA-CN or TBA-OH (11 mmol) in MeCN (10 ml) is added dropwise over 20–30 min to the haloalkane (10 mmol) and Me₂C(OH)CN (1.3 g, 15 mmol) in MeCN (20 ml) and the mixture is stirred until TLC analysis indicates the reaction to be complete. The mixture is evaporated and the residue taken up in H₂O (10 ml) and Et₂O (40 ml). The organic phase is separated, washed with H₂O (3 × 5 ml), dried (MgSO₄), and evaporated to yield the nitrile.

Acetone cyanhydrin has been used as a convenient source of cyanide ion for the preparation of alkyl cyanides (6.1.1.E) [21]. Moderate yields (50–77%) have been achieved using tetra-*n*-butylammonium cyanide or hydroxide as the base.

TABLE 6.1

Selected examples of the conversion of haloalkanes into alkyl cyanides

Haloalkane	Reaction conditions	% yield
<i>n</i> -BuBr	6.1.1.A/6 h/90°C ^a	71
<i>n</i> -C ₈ H ₁₇ Cl	6.1.1.B/8 h/85°C	75
<i>n</i> -C ₈ H ₁₇ Br	6.1.1.B/8 h/85°C	97
<i>n</i> -C ₈ H ₁₇ I	6.1.1.B/8 h/85°C	45
<i>n</i> -C ₆ H ₁₃ CHBrMe	6.1.1.B/20 h/85°C	72
PhCH ₂ Cl	6.1.1.A/1 h/95°C ^a	89
PhCH ₂ Br	6.1.1.B/2 h/rt	99
Ph(CH ₂) ₂ Br	6.1.1.A/6 h/95°C ^a	92
Br(CH ₂) ₂ CN	6.1.1.A/1.5 h/70°C ^a	50
Cl(CH ₂) ₂ Cl	6.1.1.A/4 h/80°C ^a	40
Br(CH ₂) ₃ Cl	6.1.1.B/24 h/rt	94 ^b
Br(CH ₂) ₃ Br	6.1.1.A/3 h/95°C ^a	71
	6.1.1.B/8 h/rt	98
[Cl(CH ₂) ₂] ₂ S	6.1.1.A/3 h/80°C ^c	~100

^a Using TMBA-Cl. ^b Cl(CH₂)₃CN. ^c Using TBBA-Cl.

Unsaturated nitriles have been obtained from the S_N reaction of 3-chloroalk-1-enes [22] using tetra-*n*-butylammonium iodide as the catalyst. Under the basic reaction conditions, isomerism occurs such that not only is the 1-cyanoalk-2-ene obtained, but also the conjugated 1-cyanoalk-1-ene. Surprisingly, when tetra-*n*-butylammonium chloride is used, direct S_N displacement of the chloro group occurs, followed by isomerization, to give the 3-cyanoalk-2-ene.

6.1.2 Cyanoalkenes

The β -chloroalkene (10 mmol) NaCN (0.98 g, 20 mmol), TBA-Cl or TBA-I (0.4 mmol) and H₂O (0.28 g) are heated at 90–110°C for 2 h. Et₂O (40 ml) and H₂O (20 ml) are added and the aqueous phase is separated and extracted with Et₂O (40 ml). The combined ethereal solutions are washed with H₂O (2 \times 20 ml), or aqueous Na₂S₂O₄ (sat. soln. 20 ml) when TBA-I is used, dried (MgSO₄), and fractionally distilled to yield the cyanoalkenes RC(CN)=CMe₂, **A**; RCH=CMeCH₂CN, **B**; RCH₂CMe=CHCN, **C** (Table 6.2).

α -Iminonitriles are obtained in good yield from the reaction of imidoyl chlorides with potassium cyanide, when the (essentially) solid:liquid reaction is catalysed by quaternary ammonium salts [23].

TABLE 6.2
Selected examples of the formation of cyanoalkenes by S_N reactions

RCHClCMe=CH ₂	Catalyst	Reaction conditions	% conversion	Product ratio A:B:C
R = PhCH ₂	TBA-I	6.1.2/110°C/2 h	81	0:24:76
<i>n</i> -C ₅ H ₁₁	TBA-I	6.1.2/110°C/3 h	85	5:0:95
Me ₂ C=CHCH ₂	TBA-I ^a	6.1.2/90°C/2 h	77	0:16:84

^a 100% conversion into **A**, when TBA-Cl used at 90°C over 13.5 h.

6.1.3 α -Iminonitriles, ArC(CN)=NPh

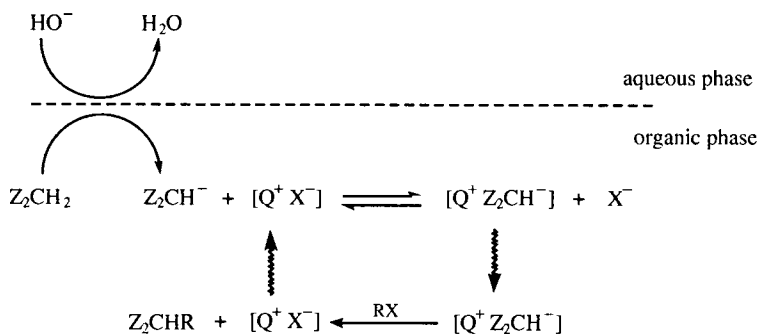
The *N*-phenyl benzimidoyl chloride (10 mmol) in CHCl₃ (50 ml) is stirred for 24 h with KCN (1.95 g, 30 mmol) and HDTMA-Br (1.5 mmol) with a trace amount of H₂O. The mixture is washed with H₂O (2 \times 25 ml), dried (MgSO₄), and chromatographed to yield the nitrile [e.g. from ArC(Cl)=NPh: Ar = Ph, 8%; 4-MeC₆H₄, 68%, 4-ClC₆H₄, 80%; 4-MeOC₆H₄, 79%].

Aroyl cyanides, which have low stability in the presence of water, can be prepared under phase-transfer catalytic conditions in yields >60% [24]. A major by-product of the reaction with benzoyl chloride is α,α -dicyanobenzyl benzoate, resulting from reaction of the benzoyl cyanide with the cyanide ion and subsequent esterification.

6.1.4 Aryl cyanides

NaCN (18 g) in H₂O (20 ml) is stirred with the aryl chloride (0.36 mol) and TBA-Br (0.1 g, 0.3 mmol) in CH₂Cl₂ (300 ml) at 0°C for *ca.* 1 h. The mixture is filtered and the organic phase is separated, dried (MgSO₄), and evaporated to yield the aryl cyanide.

Owing to their low acidity, ‘classical’ reactions of carbanions usually require their formation by the action of very strong bases (e.g. NaH or *i*-Pr₂NLi) under strictly anhydrous conditions. Reactions conducted in hydroxylic solvents are invariably at equilibrium and require continual removal of the product to enable the reaction to go to completion. In contrast, the corresponding reactions under phase-transfer catalytic conditions can be conducted in the presence of water, as the reactive carbanionic species is retained in the organic phase as an ion pair with the quaternary ammonium cation. As indicated in Chapter 1, water is not transferred across the phase boundary (particularly from strongly basic aqueous media) and, as hydroxide ions are also not readily transferred by most quaternary ammonium salts, water is not generated in the organic phase through their reaction with the active methylene compounds. The mechanism of reactions leading to the formation of C–C bonds, therefore, is effectively the interfacial formation of the carbanion with its solubilization and subsequent reaction in the organic phase by the formation of the ion-pairs (Scheme 6.1).



Scheme 6.1

The following sections of this chapter provide a representative sample of reactions leading to C–C bond formation. The lists of references are not exhaustive and the procedures are typical for the type of reaction. Reactions involving carbenes are discussed in Chapter 7.

Early procedures used stoichiometric amounts of the quaternary ammonium catalyst to solubilize the preformed sodium or potassium salts of the active methylene compounds (prepared under anhydrous conditions) in the organic medium. Subsequently, liquid:liquid two-phase procedures using catalytic amounts of the quaternary ammonium salts were developed, and solid:liquid two-phase conditions have been used to improve yields. In some cases, only the solid:liquid two-phase procedures are effective.

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6.2 ALKYLATION AND ACYLATION OF ACTIVATED METHYLENE GROUPS

Whereas alkylation of activated methylene systems by classical methods produces a mixture of mono- and dialkylated products, with the latter frequently predominating, phase-transfer catalytic procedures permit better control and it is possible to obtain only the monoalkylated derivatives. Extended reaction times or more vigorous conditions with an excess of the alkylating agent lead to dialkylated products or, with dihaloalkanes, carbocyclic compounds as the technique mimics dilute concentration conditions, e.g. the resonance stabilized cyclopentadienyl anion, generated under solid:liquid two-phase conditions, or under liquid:liquid conditions, reacts with 1,2-dihaloethanes to form spiro[2,4]hepta-4,6-diene (70–85%) [1–3]. Reaction with dichloromethane produces bis(cyclopenta-2,4-dien-1-yl)methane (60%) [4].

The low acidity of methylene groups, which are activated by only one electron-withdrawing mesomeric substituent, generally results in a lower reactivity under phase-transfer catalytic conditions. Monoalkylation normally occurs, sometimes to the complete exclusion of dialkylation, and further alkylation is generally only

feasible by using more vigorous conditions or prolonged reaction times. Liquid:liquid two-phase alkylation by secondary haloalkanes and α,ω -dihaloalkanes is more difficult than for primary haloalkanes [e.g. 5].

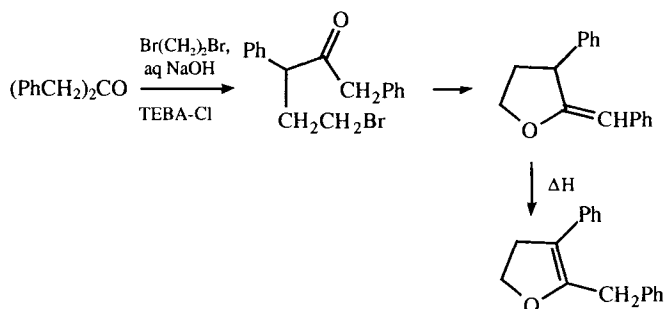
Simple aliphatic nitriles, aldehydes, ketones and esters are not readily alkylated under liquid:liquid phase-transfer conditions. Direct alkylation of aldehydes under even mildly basic phase-transfer conditions has to compete with aldol and Cannizzaro reactions and yields are low and variable [e.g. 6]. α,α -Disubstituted aldehydes are *C*-alkylated, e.g. formylcyclohexane has been alkylated (>70%) with a range of reagents using benzyltrimethylammonium isopropoxide as the basic catalyst [7], whereas α -unsubstituted alkanals tend to undergo aldol condensation under basic liquid:liquid two-phase conditions [8].

In the main, the original 'extractive alkylation' procedures of the late 1960s, which used stoichiometric amounts of the quaternary ammonium salt, have now been superseded by solid-liquid phase-transfer catalytic processes [e.g. 9–13]. Combined solid:liquid phase-transfer catalysis and microwave irradiation [e.g. 14–17], or ultrasound [13], reduces reaction times while retaining the high yields. Polymer-supported catalysts have also been used [e.g. 18] and it has been noted that not only are such reactions slower but the order in which the reagents are added is important in order to promote diffusion into the polymer.

Although iodoalkanes cannot be used under normal liquid:liquid two-phase conditions, their use is acceptable under solid:liquid two-phase conditions in the absence of an organic solvent (see Chapter 1.2) [12]. Benzylic halides generally react more readily [e.g. 19, 20] than simple haloalkanes, particularly when substituted at the *para*-position by an electron-withdrawing group which increases the acidity of the methylene group and stabilizes the carbanion [e.g. 14, 21]. The methylene group is further activated when the aryl ring is complexed with chromium tricarbonyl, the electron-withdrawing effect of which enhances the C-H acidity [22, 23]. The technique has been used with advantage for the *C*-alkylation of phenylacetic esters and related compounds and has the additional bonus that the complexed chromium directs the approach of the alkylating agent to the carbanionic centre and has potential in chiral synthesis.

2-Tetralone is readily mono- or di-alkylated at the 1-position to the exclusion of *O*-alkylation with a range of alkylating agents under liquid:liquid two-phase conditions without an added solvent [24]. Similarly, it has been reported that anthrone undergoes mono- and di-*C*-alkylation at the 10-position with propargyl and allyl halides to the almost complete exclusion of *O*-alkylation [25]. It has been claimed that methylation yields 9-methoxyanthracene [26].

1,2-Dibromoethane normally reacts with activated methylene groups to produce cyclopropyl derivatives [e.g. 25, 27], but not with 1,3-diphenylpropanone. Unlike the corresponding reaction of 1,3-dibromopropane with the ketone to form 2,6-diphenylcyclohexanone, 1,2-dibromoethane produces 2-benzylidene-3-phenyl-tetrahydrofuran and the isomeric 2-benzyl-3-phenyl-4,5-dihydrofuran via initial *C*-alkylation followed by ring closure onto the carbonyl oxygen atom (Scheme 6.2) [28].



6.2.1 2-Benzyl-3-phenyl-4,5-dihydrofuran

(PhCH₂)₂CO (4.2 g, 20 mmol), Br(CH₂)₂Br (5.6 g, 30 mmol) and TEBA-Cl (0.16 g, 0.7 mmol) are stirred for 3 h with aqueous NaOH (50%, 10 ml) at 60 °C (the reaction is initially exothermic). The mixture is poured into H₂O (100 ml) and extracted with CH₂Cl₂ (3 × 100 ml). The combined extracts are washed well with H₂O, dried (MgSO₄), and evaporated. Distillation of the initially formed tetrahydrofuran yields 2-benzyl-3-phenyl-4,5-dihydrofuran and 2-benzylidene-3-phenyltetrahydrofuran (2.6 : 1, 76%).

1-Chloro-4-cyanobutane undergoes a high-yielding intramolecular cyclization under basic solid:liquid two-phase conditions in the presence of tetra-*n*-butylammonium chloride to form cyclobutyl cyanide; 1-chloro-4,8-dicyanooctane is formed as a by-product (*ca.* 10%). No cyclization occurs in the absence of the ammonium salt or when aqueous sodium hydroxide is used [29]. Attempts to produce the cyclobutyl derivative in a one-pot reaction of 1,4-dichlorobutane with sodium cyanide/sodium hydroxide gave only a 9% yield, with 1,4-dicyanobutane (63%) and 1-chloro-4-cyanobutane (18%). A similar intramolecular cyclization of (3-chloropropylthio)acetonitrile yields 2-cyanotetrahydrothiophene (80%) [30].

The intramolecular cyclization of γ -chloro esters, which normally requires strongly basic anhydrous conditions, is accomplished in high yield with aqueous sodium hydroxide and tetra-*n*-butylammonium bromide in toluene [31]. Poor yields result when dichloromethane is used as the solvent.

6.2.2 Typical liquid:liquid alkylation of methylene groups activated by a carbonyl or nitrile group

Method A: Aqueous NaOH (50%, 100 ml) is added to TEBA-Cl (23 mg, 0.1 mol) and the methylene compound (0.1 mol) and the mixture is stirred at room temperature for 15 min. The alkylating agent (0.2 mol) in CH₂Cl₂ or PhH (100 ml) is then added dropwise and the two-phase system is stirred for 10–30 min at *ca.* 50 °C. The organic phase is then separated, dried (MgSO₄), and evaporated. Et₂O (50 ml) is added to the residue and the ethereal solution is filtered and evaporated to yield the alkylated product.

Method B: Aqueous NaOH (50%, 5 ml) is added to the methylene compound (7.7 mmol) and TBA-HSO₄ (0.26 g, 8 mmol) in *n*-C₆H₁₄ or CH₂Cl₂ (10 ml). The alkylating agent is

introduced via a syringe over 30 min at 0–5°C and the mixture is stirred for 15 min at 10–15°C. The mixture is then diluted with H₂O (40 ml), and the aqueous phase is then separated and extracted with Et₂O (2 × 15 ml). The combined organic solutions are washed with H₂O (2 × 15 ml), dried (MgSO₄), and evaporated to yield the monoalkylated product.

Method C (solid:liquid process): The methylene compound (25 mmol), powdered KOH (2.8 g) and TBA-Br (80 mg, 0.25 mmol) are stirred at room temperature for 1 h. The alkylating agent (25 mmol) is added dropwise and the mixture is stirred at ca. 30°C until the reaction is complete, as shown by TLC analysis. The mixture is extracted with Et₂O (2 × 50 ml) and the extracts are evaporated to yield the alkylated product.

Method D (using microwave irradiation): TBA-F (0.26 g, 1 mmol) on alumina (1.7 g) is added to the methylene compound (1.5 mmol) and alkylating agent (1.1 mmol) in the minimum amount of THF or Et₂O and the mixture is evaporated to dryness, powdered and irradiated at 300 W for 3–7 min. The solid is extracted with Et₂O and the extracts are fractionally distilled to yield the alkylated product.

Method E (using microwave irradiation): An intimate mixture of the methylene compound (0.15 mol), the alkylating agent (0.15–0.2 mol), TEBA-Cl (15 mmol) and powdered NaOH (0.55 mol) are irradiated at 350 W for 1–3 min. The product is isolated using the procedure described in 6.2.2.D.

Method F: The haloalkane (0.25 mmol) is added to the Cr(CO)₃-complex of the phenylacetic ester (0.25 mmol) in CH₂Cl₂ (5 ml) and CTA-Br (36 mg, 0.1 mmol) in aqueous NaOH (50%, 5 ml). The mixture is stirred at room temperature until the reaction is complete, as indicated by TLC analysis, and the organic phase is then separated, washed well with water, dried (Na₂SO₄), and evaporated to yield the C-alkylated derivative (70–100%).

Method G (using ultrasound): The methylene compound (10 mmol), TBA-Br (32 mg, 0.1 mmol) and powdered KOH (1.7 g) are subjected to ultrasound (50 Hz, 150 W) for 20 min. The mixture is cooled to 0°C and the haloalkane (40 mmol) is added and the mixture stirred at room temperature. The alkylated product is isolated using the procedure described in 6.2.2.D.

6.2.3 Cyclobutyl cyanide

TBA-Cl (1.26 g, 4.5 mmol) and NaOH (7.2 g, 0.18 mol) are added to 1-chloro-4-cyanobutane (10.6 g, 90 mmol) in THF (100 ml) and the mixture is stirred under reflux for 6 h. Fractional distillation yields cyclobutyl cyanide (6.5 g, 90%).

6.2.4 1,4-Dicyanobutane

NaCN (0.49 g, 10 mmol), NaOH (0.3 g, 7.5 mmol) and TBA-Br (0.16 g, 0.5 mmol) are added to Cl(CH₂)₄Cl (0.63 g, 5 mmol) in THF (10 ml) and the mixture is stirred under reflux for 3 h. GLC analysis indicates 90% conversion to 1,4-dicyanobutane, 1-chloro-4-cyanobutane and cyclobutyl cyanide in a 7:2:1 ratio.

6.2.5 2-Cyanotetrahydrothiophene

Aqueous NaOH (50%, 327 ml) is added dropwise to a slurry of Cl(CH₂)₃SCH₂CN (73.3 g, 0.49 mol) and TEBA-Cl (3.34 g, 15 mmol). The exothermic reaction mixture is stirred for

TABLE 6.3

Selected examples of the alkylation of aliphatic nitriles, esters and ketones

Alkylating agent	Method	% monoalkylation	% dialkylation
<i>PhSCH₂CO₂Et</i>			
<i>n</i> -BuBr	6.2.2.E ^{a,b}	59	0
CH ₂ =CHCH ₂ Br	6.2.2.E ^{a,c}	67	0
PhCH ₂ Cl	6.2.2.E ^{a,d}	83	0
<i>4-O₂NC₆H₄CH₂CO₂Et</i>			
Ph(CH ₂) _{<i>n</i>} I	6.2.2.D	55–79 (<i>n</i> = 3–8)	
PhS(CH ₂) _{<i>n</i>} Br	6.2.2.D	50–59 (<i>n</i> = 6–8)	
<i>PhCH₂COMe</i>			
MeI	6.2.2.C	95	0
<i>n</i> -BuBr	6.2.2.C	92	0
CH ₂ =CHCH ₂ Br	6.2.2.C	90	0
PhCH ₂ Br	6.2.2.C	96	0
Br(CH ₂) ₂ Br	6.2.2.A	54 (cyclic product)	
<i>PhCH₂CN</i>			
MeI	6.2.2.A	72	14
EtI	6.2.2.A	90	0
EtBr	6.2.2.A	78	0
<i>i</i> -PrI	6.2.2.A	75	0
<i>n</i> -C ₆ H ₁₃ Br	6.2.2.E	70	0
CH ₂ =CHCH ₂ Br	6.2.2.E ^c	48	10
PhCH ₂ Br	6.2.2.E ^f	62	32
Br(CH ₂) ₄ Br	6.2.2.A	88 (cyclic product)	
<i>PhSCH₂CN</i>			
EtBr	6.2.2.A	80	0
<i>n</i> -BuBr	6.2.2.A	82	0
<i>PhCHMeCN</i>			
MeOCH ₂ Cl	6.2.2.A	68	0
HC≡CCl	6.2.2.B	86 ^e	0

^a KOH:K₂CO₃ (1 : 2). ^b Power level 8 for 4.5 min. ^c Power level 2 for 3.5 min. ^d Power level 3 for 4.5 min.^e Irradiation at 160 W for 3 min. / Using 0.6 mol NaOH and 1 min irradiation at 350 W. ^f HC≡CCl is prepared by Method 9.1.3.A and flushed into the reaction vessel by a stream of argon (see also 6.2.11).

ca. 1 h, and the aqueous layer is then separated, diluted with H₂O (90 ml), and extracted with PhH (90 ml). The organic extracts are washed with dilute HCl (10%, 2 × 30 ml), dried (MgSO₄), and fractionally distilled to yield the 2-cyanotetrahydrothiophene (80%).

6.2.6 Ethoxycarbonylcyclopropanes

TBA-Br (5 g, 15.5 mmol) is added to the ethyl 4-chloroalkanoate (0.1 mol) in PhMe (200 ml) and the solution is stirred at 35–40°C. Aqueous NaOH (50%, 40 ml) is added dropwise over *ca.* 1 h at <40°C. The mixture is stirred at 40°C for 2 h, then cooled to room temperature, and H₂O (150 ml) is added. The aqueous phase is separated, extracted with PhMe (2 × 30 ml), and the organic solutions are washed with aqueous HCl (0.01 M, 110 ml) and then H₂O until the washings are neutral. The dried (Na₂SO₄) solution is

evaporated to yield the cyclopropane (e.g. 91% from ethyl 4-chlorobutanoate; 86% from ethyl 4-chloro-4-methylpentanoate).

C-Alkylation of ethyl 1,3-dithiane-2-carboxylate (for preparation, see 4.1.6) under mild solid:liquid phase-transfer catalytic conditions [32, 33] provides a potentially useful route to α -ketoesters.

6.2.7 C-Alkylation of ethyl 1,3-dithiane-2-carboxylate

K₂CO₃ (5 g) is added to the dithiane (1.92 g, 10 mmol), bromoalkane (10 mmol) and Aliquat (0.4 g, 1 mmol) in PhMe (10 ml) and the mixture is stirred at 60°C for *ca.* 5 h. The mixture is filtered and the filtrate is fractionally distilled to yield the C-alkylated product (e.g. Et, 37%; *n*-Bu, 46%, CH₂=CHCH₂, 81%; PhCH₂, 74%).

Regiospecific mono-C-alkylation (60–90%) of trimethylsilyl enol ethers is promoted by benzyltriethylammonium fluoride [34, 35]. A similar alkylation of tin(IV) enolates is aided by stoichiometric amount of tetra-*n*-butylammonium bromide and has been utilized in the synthesis of γ -iminoketones [36]. Carbanions from weakly acidic carbon acids can be generated by the reaction of their trimethylsilyl derivatives with tetra-*n*-butylammonium triphenyldifluorosilicate [37] (see also Section 6.3). Such carbanions react readily with haloalkanes. Tautomeric ketones in which the enol form has a high degree of stabilization are *O*-alkylated to form the enol ether, e.g. methylation of anthrone produces 9-methoxyanthracene [26].

6.2.8 C-Alkylation of silyl enol ethers

The enol ether (1.16 mmol) and alkylating agent (1 mmol) in THF (2 ml) are stirred at room temperature for 1 h and then at 50°C for 30 min with TEBA-F (0.22 g, 1.3 mmol) and 4 Å molecular sieves (1 g) in THF (4 ml). The mixture is filtered and evaporated and the alkylated carbonyl compound is purified by chromatography from silica gel.

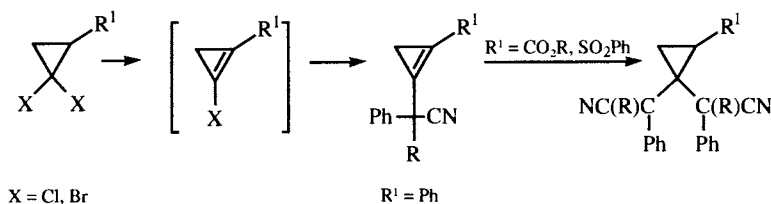
6.2.9 γ -Iminoketones

The α -haloimine (3 mmol) is added at 25°C to the Bu₃Sn(IV) enolate (3.6 mmol) and TBA-Br (1.74 g, 5.4 mmol) in THF (3 ml) and the mixture is stirred for 1–3 h. The mixture is then evaporated and the residue is triturated with *n*-C₆H₁₄ (2 × 10 ml). Evaporation and fractional distillation gives the γ -iminoketone (50–80%).

6.2.10 C-Alkylation of carbanions generated from trimethylsilyl derivatives

The haloalkane (1 mmol), trimethylsilyl derivative (10 mmol) and TBA-Ph₃SiF₂ (1.08 g, 2 mmol) are heated at 70°C in THF (5 ml) for 24 h. Volatile material is removed under reduced pressure and the residue is extracted with Et₂O (3 × 25 ml). The extracts are washed with H₂O (2 × 50 ml) and brine (50 ml), dried (MgSO₄), and evaporated to yield the alkylated compound (e.g. 81% *n*-C₁₂H₂₅C≡CPh from PhC≡CTMS; 84% *n*-C₁₃H₂₇Ph from PhCH₂TMS; 87% *n*-C₁₃H₂₇CH=CH₂ from CH₂=CHCH₂TMS].

Phenylacetonitriles react under basic phase-transfer catalytic conditions with a range of alkylating agents [e.g. 38–40]. The reaction with 1,1-dichloroethenes produces ethynyl derivatives [41–43]; the ethene initially undergoes an elimination reaction to yield the chloroethyne, which undergoes a Michael-type reaction with the carbanion, followed by elimination of hydrogen chloride. Under mild conditions the intermediate Michael adduct can be isolated [41]. In an analogous type of reaction, phenylacetonitriles react with 1,1-dihalocyclopropanes to produce the 1-alkylated cyclopropene (Scheme 6.3) [44]. When the ring is substituted by an electron withdrawing group, a further Michael reaction occurs to produce the 1,1-dialkylated cyclopropane [45]. Other α,ω -dihaloalkanes react with phenylacetonitrile to form the cycloalkane derivatives or linear bis-nitriles in variable yields [46], whereas α -alkoxyphenylacetonitriles are C-alkylated in high yield and provide useful precursors for aryl ketones and acrylonitriles [47]. Acetonitriles can also be alkylated in good yield (>70%) under triphase catalytic conditions using Dowex 44 [39].



Scheme 6.3

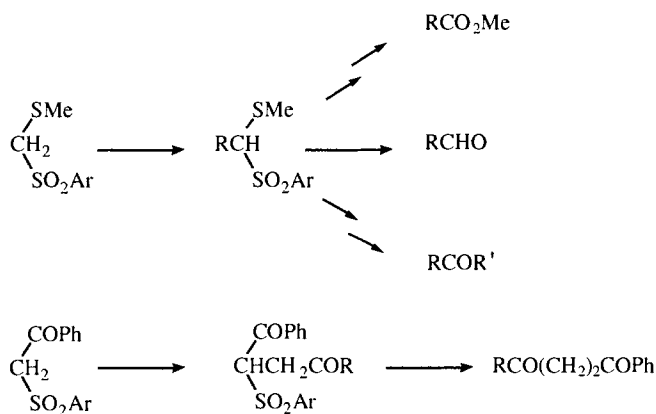
6.2.11 2-Ethynyl-2-phenylacetonitriles

Caution: This reaction must be conducted under an inert atmosphere to prevent violent combustion of the chloroethyne, if it comes in contact with the air. Aqueous NaOH (60%, 12.5 ml) is added via a syringe to the phenylacetonitrile, Ph(R)CHCN (3.5 mmol), $\text{Cl}_2\text{C}=\text{CH}_2$ (0.61 g, 3.5 mmol) and TBA- HSO_4 (12 mg, 0.035 mmol) in Et_2O (7 ml) in an enclosed vessel with stirring at 35°C . The mixture is stirred for a further 3–5 h and H_2O (10 ml) is then added. The aqueous phase is separated, extracted with Et_2O (2×15 ml) and the combined organic phases are washed with H_2O (2×10 ml), dried (MgSO_4), and evaporated to yield the ethynyl derivative, $\text{PhC}(\text{C}\equiv\text{CH})(\text{R})\text{CN}$ (e.g. $\text{R} = \text{Me}$, 2 h, 61%; Et , 3 h, 81%; PhCH_2 , 5 h, 89%; $\text{CH}_2=\text{CHCH}_2$, 5 h, 72%).

6.2.12 2-(Cycloprop-1-enyl)-2-phenylacetonitriles

The phenylacetonitrile (18 mmol) and 1,1-dibromo-2-phenylcyclopropane (4.1 g, 15 mmol) are stirred with aqueous NaOH (50%, 12 ml) and TEBA-Cl (0.29 g, 0.9 mmol) at 45°C . The mixture is cooled to room temperature, H_2O (50 ml) is added, and is extracted with CH_2Cl_2 (3×50 ml). The extracts are washed sequentially with H_2O (50 ml), aqueous HCl (2%, 50 ml) and H_2O (50 ml), dried (MgSO_4), and evaporated to yield the cyclopropene (e.g. from PhCHRCN : $\text{R} = \text{Me}$, 9 h, 55%; Et , 8 h, 56%; $\text{CH}_2=\text{CHCH}_2$, 6 h, 28%; PhCH_2 , 4 h, 31%).

Methylenesulphones are more acidic than the simple esters, ketones and cyano compounds and are more reactive with haloalkanes [e.g. 48–57] to yield precursors for the synthesis of aldehydes [53], ketones [53], esters [54] and 1,4-diketones [55] (Scheme 6.4). The early ‘extractive alkylation’ methods have been superseded by solid:liquid phase-transfer catalytic methods [e.g. 58] and, combined with microwave irradiation, the reaction times are reduced dramatically [59]. The reactions appear to be somewhat sensitive to steric hindrance, as the methylenesulphones tend to be unreactive towards secondary haloalkanes and it has been reported that iodomethylsulphones cannot be dialkylated [49], although mono- and dichloromethylsulphones are alkylated with no difficulty [48, 60] and methylenesulphones react with dihaloalkanes to yield cycloalkyl sulphones (Table 6.5 and 6.6). When the ratio of dihaloalkane to methylene sulphone is greater than 0.5 : 1, open chain systems are produced [48, 49]. Vinyl sulphones are obtained from the base-catalysed elimination of the halogen acid from the products of the alkylation of halomethylenesulphones [48].



Scheme 6.4

Sulphonylacetic esters are converted in a one-pot reaction into cinnamic esters, when alkylated with benzyl halides [50].

6.2.13 Alkylation of methylenesulphones (Table 6.4)

Method A: TBA-Br (3.22 g, 10 mmol) in aqueous NaOH (2M, 5 ml) is added dropwise to the methylenesulphone (10 mmol) in CHCl_3 (17 ml) and the mixture is stirred for 30 min at 20°C. The organic phase is separated, dried (MgSO_4), and added to the alkylating agent (10 mmol) in CHCl_3 (5 ml). The mixture is allowed to stand at room temperature for 40 min and is then evaporated under reduced pressure. The residue is extracted with Et_2O (4 × 20 ml) and the extracts are evaporated to yield alkylated sulphone.

Method B: Aliquat (0.14 g, 0.35 mmol) in aqueous NaOH (50%, 17 ml) is added to the alkylating agent (24 mmol) and the methylenesulphone (16 mmol) in PhMe (19 ml) and the mixture is stirred at 60°C for 30 h. The product is isolated as described in 6.2.13.A.

TABLE 6.4
Selected examples of the alkylation of methylene sulphones

R ¹ CH ₂ SO ₂ R ²		Haloalkane R ³ X	Reaction conditions	% yield R ¹ CHR ³ SO ₂ R ²
R ¹	R ²			
CH=CMe ₂	Ph	EtBr	6.2.13.E/1.5 h	89
CH=CMe ₂	Ph	<i>n</i> -BuBr	6.2.13.E/1.5 h	80
CMe=CMe ₂	Ph	<i>n</i> -BuBr	6.2.13.E/1.5 h	63
CMe=CMe ₂	Ph	CH ₂ =CHCH ₂ Br	6.2.13.E/1.5 h	85
CH=CMe ₂	Me	PhCH ₂ Cl	6.2.13.E/1.5 h	58
		CH ₂ =CHCH ₂ Br	6.2.13.E/1.5 h	79
CH=C(CN)NH ₂	Ph	<i>n</i> -Bromoalkanes	6.2.13.C/2 h	70–76 ^a
COPh	Me	PhCOCH ₂ Br	6.2.13.A/30 min	80
		MeCOCH ₂ Br	6.2.13.A/30 min	81
CN	4-MeC ₆ H ₄	MeI	6.2.13.D/3 h	95
		EtI	6.2.13.D/3 h	90 ^b
		<i>n</i> -BuBr	6.2.13.D/4 h	75
		CH ₂ =CHCH ₂ Cl	6.2.13.D/1.5 h	75
		PhCH ₂ Br	6.2.13.D/1.5 h	80
CO ₂ Et	Ph	<i>n</i> -BuBr ^c	6.2.13.H/3 min	83
		<i>n</i> -C ₈ H ₁₇ Br	6.2.13.H/3 min	79
		PhCH ₂ Cl ^d	6.2.13.H/3 min	76
CO ₂ Et	4-MeC ₆ H ₄	EtBr	6.2.13.D/4 h	81
		CH ₂ =CHCH ₂ Br	6.2.13.D/2 h	76
		HC≡CCH ₂ Br	6.2.13.D/2 h	73
MeS	4-MeC ₆ H ₄	<i>n</i> -C ₁₂ H ₂₅ Br	6.2.13.B/30 h	83
		PhCH ₂ Br	6.2.13.B/30 h	80
		<i>n</i> -BuCH=CHCH ₂ Br	6.2.13.B/2 days	75
		<i>n</i> -C ₆ H ₁₃ CH=CHCH ₂ Br	6.2.13.B/2 days	77
		<i>n</i> -C ₁₀ H ₂₁ CH=CHCH ₂ Br	6.2.13.B/3 days	77
I	Ph	EtBr	6.2.13.A/2 h	71
		<i>n</i> -BuBr	6.2.13.A/2.5 h	74
		PhCH ₂ Cl	6.2.13.A/2 h	89
Br	4-MeC ₆ H ₄	EtBr	6.2.13.A/1 h	67
		<i>n</i> -BuBr	6.2.13.A/1 h	68
Cl	4-MeC ₆ H ₄	PhCH ₂ Cl	6.2.13.A/1 h	60

^a Yields recorded for derived carboxylic ester. ^b 80% using EtBr over 2 h. ^c 10 mmol. ^d 7 mmol.

Method C: The methylenesulphone (7.4 mmol), alkylating agent (7.4 mmol) and Aliquat (0.4 g, 1 mmol) in THF (6 ml) are added to powdered KOH (1.0 g, 18 mmol) in THF (4 ml) and the mixture is stirred at room temperature for 2 h. The mixture is filtered through alumina and the filtrate is evaporated under reduced pressure to yield the alkylated product.

Method D: The methylenesulphone (5 mmol), anhydrous K₂CO₃ (1.03 g), and TEBA-Cl (0.1 g, 0.45 mmol) in MeCN (4 ml) are stirred for 15 min at room temperature, and the alkylating agent (5 mmol) is then added. The mixture is stirred at 40 °C and then poured into H₂O (30 ml). The aqueous solution is neutralized with aqueous HCl and extracted with CHCl₃ (3 × 15 ml). The dried (Na₂SO₄) extracts are evaporated to yield the alkylated product.

Method E: The methylenesulphone (15 mmol), alkylating agent (30 mmol) and TBA-Br (0.24 g, 0.75 mmol) in HMPT (1.8 ml) are added to aqueous NaOH (50%, 15 ml) and the mixture is stirred at 30–35°C for *ca.* 1.5 h. The mixture is then diluted with H₂O (50 ml) and the aqueous mixture is extracted with CHCl₃ (3 × 50 ml). The extracts are washed sequentially with dilute HCl, H₂O, and brine, dried (MgSO₄), and evaporated to give the alkylated product.

Method F (reaction with dihaloalkanes to give open-chain products): The dihaloalkane (0.01 mol) in PhH (5 ml) is added dropwise to the methylenesulphone (0.02 mol), TEBA-Cl (0.2 g, 0.8 mmol) in PhH and aqueous NaOH (50%, 15 ml). The mixture is stirred at 25–30°C for *ca.* 3 h and is then poured into H₂O (150 ml) and extracted with CH₂Cl₂ (3 × 30 ml). The extracts are washed well with H₂O, dried (MgSO₄), and evaporated to yield the open-chain systems.

Method G (reaction with dihaloalkanes to give cyclic products): The methylenesulphone (0.01 mol), TEBA-Cl (0.1 g, 0.4 mmol) in the dihaloalkane (0.011 mol) and aqueous NaOH (50%, 15 ml) are stirred at 25–30°C for 1–3 h. The reaction mixture is then poured into H₂O (100 ml) and the product is isolated as described in 6.2.13.F.

Method H (with microwave irradiation): An intimate mixture of the methylenesulphone (5 mmol), alkylating agent (5 mmol), TEBA-I (0.23 g, 1 mmol) and anhydrous K₂CO₃ (3 g, 22 mmol) is irradiated on low power using a 960 W microwave oven for 2–3 min. The product is isolated using the procedure described in 6.2.13.A.

6.2.14 Styrylsulphones

The bromomethylsulphone (8 mmol) and TEBA-Cl (0.05 g, 0.22 mmol) in aqueous NaOH (50%, 15 ml) are stirred with PhCH₂Cl (1.1 g, 8.8 mmol) at 85–90°C for 1 h. The mixture is then poured into H₂O and the styryl sulphone is isolated as described in 6.2.13.F.

6.2.15 One-pot synthesis of cinnamic esters from methyl phenylsulphinylacetate (PhSOCH₂CO₂Me)

PhSOCH₂CO₂Me (1 g, 5 mmol), K₂CO₃ (2 g) and Aliquat (0.4 g, 1 mmol) in DMF (4 ml) are stirred vigorously at room temperature for 30 min. The benzyl halide (7 mmol) and a

TABLE 6.5
Selected examples of the alkylation of methylenesulphones with dihaloalkanes

Sulphone	Dihaloalkane	Reaction time	% yield
4-MeC ₆ H ₄ SO ₂ CH ₂ Br	Br(CH ₂) ₂ Br	1 h	73
4-MeC ₆ H ₄ SO ₂ CH ₂ I	Br(CH ₂) ₂ Br	2 h	68
PhSO ₂ CH ₂ I	Br(CH ₂) ₂ Br	2 h	54
PhSO ₂ CH ₂ I	Br(CH ₂) ₄ Br	2.5 h	37
PhSO ₂ CH ₂ I	1,2-(BrCH ₂) ₂ C ₆ H ₄	3 h	39

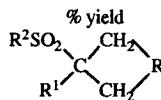
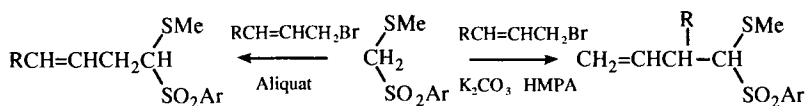


TABLE 6.6
Selected examples of the alkylation of dihalomethylenesulphones

Sulphone	Haloalkane	% yield	Sulphone	Haloalkane	% yield
PhSO ₂ CHCl ₂	EtBr	72	PhSO ₂ CHBr ₂	PhCH ₂ Cl	75
PhSO ₂ CHCl ₂	PhCH ₂ Cl	84	PhSO ₂ CHCl ₂	Br(CH ₂) ₄ Br	87 ^a

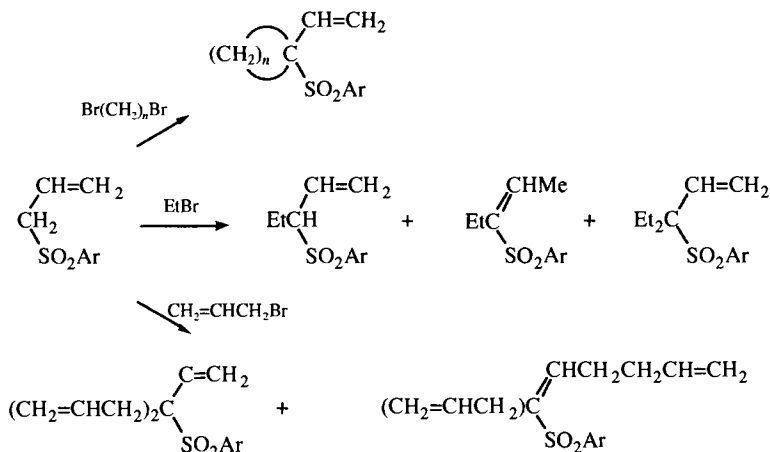
^a PhSO₂C(Cl)₂(CH₂)₄C(Cl)₂SO₂Ph.

crystal of KI in DMF (2 ml) are added and the mixture is stirred at *ca.* 60°C for 9 h, then cooled to room temperature, poured into H₂O (50 ml), neutralized with aqueous HCl, and extracted with CHCl₃ (3 × 15 ml). The dried extracts are evaporated to yield the cinnamic ester [e.g. ArCH=CHCO₂Me: Ar = Ph, 72%; 4-MeOC₆H₄, 75%; 4-MeC₆H₄, 93%; 4-ClC₆H₄, 91%; 4-MeCOC₆H₄, 70% (in MeCN); 4-EtO₂CC₆H₄, 86% (in MeCN)].



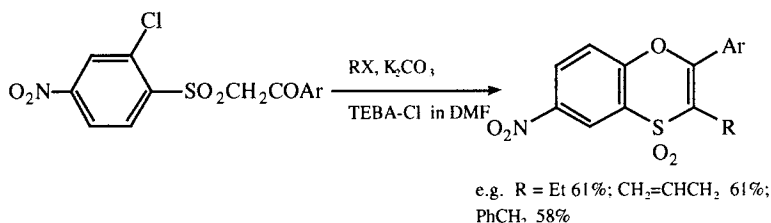
Scheme 6.5

The reaction of methylenesulphones with allyl halides in the presence of quaternary ammonium salts produces the 1-allyl derivatives [52], unlike the corresponding reaction in the absence of the catalyst in which the S_N' product is formed (Scheme 6.5). In contrast, alkylation of resonance stabilized anions derived from allyl sulphones produces complex mixtures [51] (Scheme 6.6). Encumbered allyl sulphones (e.g. 2-methylprop-2-enyl sulphones) tend to give the normal monoalkylated products. Methylene groups, which are activated by two benzenesulfonyl substituents, are readily monoalkylated; hydride reduction leads to the dithioacetal and subsequent hydrolysis affords the aldehyde [61].



Scheme 6.6

Acylmethylenesulphonylarenes, where there is judiciously placed *o*-chloro substituent on the aryl ring, undergo normal C-alkylation followed by ring closure by $S_{\text{Ar}}\text{N}$ substitution of the *o*-chloro group (Scheme 6.7) [62]. Yields of the benzoxathiin-4,4-dioxides are generally moderate (55–70%).



Scheme 6.7

6.2.16 Concerted alkylation and ring-closure of acylmethylenesulphonylarenes

The bromo or iodoalkane (4.5 mmol) in DMF (2 ml) is added to the methylenesulphone (3 mmol), K_2CO_3 (0.83 g) and TEBA-Cl (50 mg, 0.22 mmol) in DMF (5 ml) and the mixture is stirred at 70°C for *ca.* 1.5 h. H_2O (20 ml) is added to the cooled mixture and the solution is neutralized with aqueous HCl. The aqueous solution is extracted with CHCl_3 (3 × 15 ml) and the combined extracts are washed well with H_2O , dried (MgSO_4), and concentrated. The benzoxathiin-4,4-dioxide is isolated after chromatography from silica.

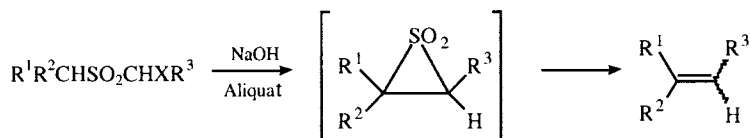
Catalysed alkylation of tosylmethylisocyanate (TOSMIC) [63, 64] has extended its versatility in the preparation of 1,4-dicarbonyl compounds and as a 1,3-dipolar precursor for the synthesis of heterocyclic compounds. The alkylation reactions should not be conducted in carbon disulphide, as nucleophilic attack by the methylene group on the carbon disulphide leads, after ring closure and *S*-alkylation, to a 4-alkylthio-1,3-thiazole system [65].

6.2.17 Alkylation of TOSMIC

Method A (in the absence of CS_2): TOSMIC (0.97 g, 5 mmol), the alkylating agent (5.5 mmol) and TBA-Br (0.32 g, 1 mmol) in CH_2Cl_2 (15 ml) are stirred at 0°C with aqueous NaOH (35%, 12 ml) for 3 h and then at room temperature for 6 h. The mixture is poured into H_2O (20 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The organic extracts are washed well with H_2O , dried (Na_2SO_4), and evaporated to yield the alkylated derivative.

Method B (in the presence of CS_2): TBA-Br (3.45 g, 11 mmol) in aqueous NaOH (10%, 10 ml) is added to TOSMIC (1.95 g, 10 mmol) in CS_2 (5 ml) and CHCl_3 (10 ml). The mixture is stirred at room temperature until all of the TOSMIC is consumed. The organic phase is separated, washed with H_2O (2 × 20 ml), dried (MgSO_4), and the haloalkane* (20 mmol) in CHCl_3 is added. The 4-alkylthio-1,3-thiazole (~90%) is isolated using the procedure described on 6.2.17.A (* reaction with an acyl halide yields the thioester).

The Ramberg–Bäckland rearrangement of α -halosulphones to alkenes (Scheme 6.8), for which the choice of base and solvent for optimum yield by classical methods is not trivial, is extremely conveniently conducted under phase-transfer catalytic conditions [66]. The reaction is particularly facile for benzylsulphones and generally gives high yields in relatively short reaction times for a range of systems. In the absence of the catalyst no reaction occurs under the mildly basic conditions.



Scheme 6.8

6.2.18 Ramberg–Bäckland synthesis of alkenes

The α -halosulphone (0.1 mol) in CH_2Cl_2 (340 ml) is stirred with aqueous NaOH (10 or 20%, 170 ml) and Aliquat (4.0 g, 10 mmol). When the reaction is complete (Table 6.7), as shown by TLC analysis, the organic phase is separated, washed well with H_2O , dried (MgSO_4), and fractionally distilled to yield the alkene.

TABLE 6.7
Ramberg–Bäckland synthesis of alkenes

$\text{R}^1\text{R}^2\text{CHSO}_2\text{CHXR}^3$				NaOH	Reaction conditions	% yield
R^1	R^2	R^3	X			
$n\text{-C}_5\text{H}_{11}$	H	H	Cl	20%	30 h/reflux	86
	$-(\text{CH}_2)_5-$	H	Cl	20%	30 h/reflux	85
Ph	H	H	Cl	10%	1.5 h/rt	82
Ph	H	CO_2Et	Br	10%	2 h/rt	75
Ph	H	Ph	Br	10%	2 h/rt	89
Ph	H	Ph	H	10%	1.5 h/reflux	94

Phosphonates and related compounds, which can subsequently be used in the Wittig–Horner reaction (see Section 6.5), are readily alkylated in good yield (Table 6.8) [67–71]. Mono-alkylation is observed with mildly basic conditions at 45°C [67] and dialkylation under stronger basic conditions at 60°C [70]. Reaction of α,ω -dihaloalkanes with phosphonocarboxylates leads to cycloalkylphosphonates [72]. The methylenebisphosphonate reacts in a similar manner.

Subsequent reduction of the alkylated cyanomethylphosphonates produces β -aminoethylphosphonates. Diethyl aminomethylphosphonates are C-alkylated with a range of agents via the initial formation of the imines [73].

TABLE 6.8
Selected examples of the alkylation of phosphonates and related compounds

Substrate	Haloalkane	Method	% yield ^a
(EtO) ₂ POCH ₂ CN	MeI	6.2.19.A	80m
		6.2.19.B ^b	80d
	EtI	6.2.19.A	70m
		6.2.19.B	71d
	<i>n</i> -PrI	6.2.19.A	70m
	CH ₂ =CHCH ₂ Br	6.2.19.A	80m
		6.2.19.B	88d
	Me ₂ CH=CHCH ₂ Cl	6.2.19.B ^c	83d
	PhCH ₂ Br	6.2.19.A	30m
	PhCH ₂ Cl	6.2.19.B ^c	46d
	Br(CH ₂) ₂ Br	6.2.19.B ^c	56d
(EtO) ₂ POCH ₂ CO ₂ Et	MeI	6.2.19.A	30m ^d
(EtO) ₂ POCH ₂ CO ₂ <i>t</i> -Bu	BrCH ₂ Br	6.2.19.C	42c
	Br(CH ₂) ₂ Br	6.2.19.C	65c
	Br(CH ₂) ₃ Br	6.2.19.C	43c
(EtO) ₂ POCH ₂ N=CPh ₂	PhCH ₂ Br	6.2.19.E	90m
(Me ₂ N) ₂ POCH ₂ CN	EtI	6.2.19.F	94m
	<i>i</i> -PrI	6.2.19.F	87m
	<i>n</i> -BuI	6.2.19.F	94m
	PhCH ₂ Cl	6.2.19.D	71m
(Me ₂ N) ₂ POCHMeCN	<i>n</i> -BuBr	6.2.19.D	100m
	ClCH ₂ CN	6.2.19.D	97m
	CH ₂ Cl ₂	6.2.19.D	89m
	CH ₂ =CHCH ₂ Cl	6.2.19.D	100m
	PhCH ₂ Cl	6.2.19.D	78m

^a m, monoalkylation; d, dialkylation; c, cyclic product. ^b With 0.4 mol of MeI over 3 h reaction time.

^c With 0.2 mol of alkylating agent. ^d Low yield due to hydrolysis of ester.

Alkylation of β-oxophosphonates, using a procedure analogous to 6.2.19.A, produces both C- and O-alkylated products [74] in ratios varying from *ca.* 2 : 1 to 5 : 1 depending on the alkylating agent and the structure of the β-oxophosphonate.

6.2.19 Alkylation of phosphonates and related compounds

Method A (monoalkylation): The phosphonate (50 mmol) and the alkylating agent (55 mmol) in CH₂Cl₂ (200 ml) are added to TBA-Br (16.0 g, 50 mmol) and aqueous NaOH (0.5 M, 100 ml) and the mixture is stirred for 1 h at 45 °C. On completion of the reaction, the organic phase is separated and evaporated. The residue is triturated with Et₂O (100 ml) and the dried (MgSO₄) extract is evaporated to give the monoalkylated product.

Method B (dialkylation): Aqueous NaOH (50%, 100 ml) is stirred with TEBA-Cl (22.75 g, 0.1 mol) and is then added to the phosphonate (0.1 mol) and the alkylating agent (0.3 mol) at such a rate to maintain the temperature below 60 °C. The mixture is stirred for 1 h, diluted with H₂O (100 ml), and extracted with Et₂O (4 × 100 ml). The extracts are washed with H₂O (3 × 50 ml) and brine (50 ml), dried (MgSO₄), and evaporated to yield the dialkylated product.

Method C (formation of cycloalkanes): The phosphonate (5 mmol) in the α,ω -dibromoalkane (5 ml) is added to HTBA-Br (1.8 g, 5 mmol) in aqueous NaOH (50%, 15 ml). The mixture is stirred at room temperature for 24 h (48 h for 1,3-dibromopropane) and then poured into CH_2Cl_2 (1000 ml) and H_2O (100 ml). The organic phase is separated, washed with H_2O (6×100 ml), brine (2×100 ml), dried (MgSO_4), and evaporated to yield the cycloalkane.

Method D: The phosphoric diamide (30 mmol), alkylating agent (37 mmol) and TEA-Cl (75 mg, 3 mmol) in aqueous NaOH (50%, 75 ml) are stirred at room temperature for 3 h. The mixture is then diluted with H_2O (8 ml) and extracted with CHCl_3 (3×25 ml). The dried (MgSO_4) extracts are evaporated to yield the monoalkylated derivative.

Method E: The imine (1 mmol), Aliquat (20 mg, 0.05 mmol), the alkylating agent (1.5 mmol), and powdered KOH (0.3 g) are intimately mixed at room temperature. The mixture is extracted with CH_2Cl_2 (10 ml) and the extract is filtered through silica and evaporated to yield the monoalkylated product.

Method F: The phosphoric diamide (30 mmol) and alkylating agent (72 mmol) in CH_2Cl_2 (30 ml) are added rapidly with stirring to TBA-OH (9.3 g, 36 mmol) in aqueous NaOH (60%, 65 ml). The mixture is stirred for 30 min and then extracted with CH_2Cl_2 (2×50 ml). The dried (MgSO_4) extracts are evaporated and the residue is triturated with Et_2O (100 ml). Evaporation of the ethereal solution gives the alkylated product.

Methylene groups, which are doubly activated by carbonyl, cyano, or nitro groups, are more acidic relative to the simple monoactivated systems and are more susceptible to alkylation under mild catalytic conditions [e.g. 75–86]; in some instances potassium fluoride has been used as the base [e.g. 83]. Solid:liquid two-phase conditions in the absence of a solvent can be used to selectively alkylate malonodinitrile; further reaction with a second alkylating agent on the C-alkylated product leads to dialkyl derivatives [85]. Reaction with α,ω -dihaloalkanes produces cycloalkane-1,1-dinitriles or linear $\alpha,\alpha,\omega,\omega$ -tetranitriles [86]. The combination of microwave irradiation with a solid:liquid two-phase system generally retains the high yields of monoalkylation while reducing the reaction time [e.g. 15, 87]. As well as conventional solid:liquid phase-transfer process using a mild base with or without an added organic solvent [80, 81], nitroacetic esters have been alkylated in moderate yield using polymer-supported catalysts [88]. Dialkylation is reduced by using a 2:1 ratio of the nitro compound:alkylating agent. When strong bases are employed with non-polar solvents, initial O-alkylation and solvolysis leads to carbonyl compounds [80, 89]. Alkylation of nitroalkanes by benzyl halides follows an $\text{S}_{\text{RN}}1$ mechanism [89].

Alkylation of β -dicarbonyl compounds and β -keto esters occurs preferentially on the carbon atom, whereas acylation produces the O-acyl derivatives (see Chapter 3). There are indications that C- and O-alkylated products are produced with simple haloalkanes and benzyl halides, but only C-alkylated derivatives are formed with propargyl and allyl halides [e.g. 90]. Di-C-alkylation frequently occurs and it has been reported that the use of tetra-alkylammonium 2-oxopyrrolidinyl salts are more effective catalysts (in place of aqueous sodium hydroxide and quaternary ammonium salt) for selective (~90%) mono-C-alkylation of β -dicarbonyl compounds [91].

Alkylation of 2-ethoxycarbonylcyclohexanone, followed by hydrolysis and decarboxylation, has been used as a convenient route to 2-alkylcyclohexanones [74, 92]. Polymer-supported catalysts have also been used [e.g. 93]; 2-acylcyclohexanones are C-alkylated at the 2-position almost exclusively, whereas cyclohexane-1,3-dione produces a mixture of mono- and di-C-alkylated products, together with the O-alkylated derivative. In all cases, less polar solvents promote the O-alkylation.

Glycopyranosyl halides react with ethyl acetoacetate and pentan-2,4-dione under solid:liquid phase-transfer catalytic conditions, using potassium phosphate as the base, providing the C-alkylated derivatives (40–60%) [94].

6.2.20 Alkylation of β -dicarbonyl compounds, cyano esters and malonodinitrile (Table 6.9)

Method A ('ion-pair extraction' technique): TBA- HSO_4 (38.4 g, 0.11 mol) is added to aqueous NaOH (2 M, 100 ml) and the mixture stirred at room temperature for 5 min. The aqueous solution is added to the methylene compound (0.1 mol) in CHCl_3 (100 ml) and the two-phase system is stirred until the aqueous phase is neutral. The organic phase is separated and evaporated.

The alkylating agent (0.1 mol) is added to the TBA salt of the methylene compound (0.05 mol) in CHCl_3 (75 ml) and the slightly exothermic reaction is stirred at room temperature. Volatile material is evaporated and Et_2O (25 ml) is added to the residue. The filtered ethereal solution is evaporated to yield the alkylated product.

Method B: see 6.2.13.G.

Method C (solid:liquid conditions): NaH (3 g, 50% in oil) is washed repeatedly with PhH and then covered with PhH (200 ml). The methylene compound (50 mmol) is added dropwise and the mixture stirred until no more H_2 is evolved. Aliquat (2.0 g, 5 mmol) and the alkylating agent (0.1 mol) are added at ca. 60°C and the mixture is stirred for a further 8 h and then cooled and acidified with HCl (1M). The organic phase is separated, dried (MgSO_4), and fractionally distilled to yield the alkylated product.

Method D (solid:liquid conditions): The methylene compound (0.2 mol) and the alkylating agent (0.42 mol) are stirred for 3 h at 90°C with TEBA-Cl (0.9 g, 4 mmol) and anhydrous Na_2CO_3 (44.5 g, 0.42 mol). The mixture is cooled and H_2O (50 ml) is added. The organic phase is separated, washed well with H_2O , dried (MgSO_4), and evaporated to yield the alkylated product.

Method E (solid:liquid conditions): NaHCO_3 (3.2 g) and $\text{CH}_2(\text{CN})_2$ (1.65 g, 25 mmol) are stirred for ca. 30 min at 40°C, and TBA-Br (0.32 g, 1 mmol) and the haloalkane (25 mmol) are then added. The mixture is stirred until the reaction is complete (4–7 h) and CH_2Cl_2 (250 ml) is added. The filtered solution is evaporated to yield the crude alkylated product, which is purified by chromatography from silica.

Method F (solid:liquid conditions): *t*-BuOK (3.3 g), the methylene compound (25 mmol), and Aliquat (0.72 g, 1.5 mmol) are stirred for 15 min. The alkylating agent (25 mmol) is added dropwise and the mixture is stirred for a further 30 min. EtOAc (50 ml) is added and the mixture is filtered through Florisil. Fractional distillation of the filtrate yields the product.

Method G (solid:liquid conditions): $\text{CH}_2(\text{CN})_2$ (1.65 g, 25 mmol), the haloalkane or α,ω -dihaloalkane (12 mmol) and TBA-Br (1.65 g, 1 mmol) are stirred for 30 min and K_2CO_3 or *t*-BuOK (12 mmol) is added. The mixture is stirred at 0°C for 5–24 h. The crude

TABLE 6.9

Selected examples of the mono- and dialkylation of β -dicarbonyl compounds, cyano esters and malonodinitrile

Haloalkane	Reaction conditions	% yield	
		Monoalkylation	Dialkylation
<i>With MeCOCH₂CO₂Me</i>			
MeI	6.2.20.A/10 min/rt	80	10
EtI	6.2.20.A/20 min/rt	83.5	9
<i>i</i> -PrI	6.2.20.A/2 h/rt	90 ^b	5
<i>n</i> -BuI	6.2.20.A/1 h/rt	90	5
CH ₂ =CHCH ₂ Br	6.2.20.C/8 h/50–60 °C	85	–
CH ₂ =CHCH ₂ Cl	6.2.20.C/8 h/50–60 °C	30	–
Me ₂ C=CHCH ₂ Cl	6.2.20.C/8 h/50–60 °C	37	–
<i>With MeCOCH₂CO₂Et</i>			
<i>n</i> -BuBr	6.2.20.G/4.5 min/89 °C	61	–
CH ₂ =CHCH ₂ Br	6.2.20.G/3 min/75 °C	81	–
PhCH ₂ Cl	6.2.20.C/8 h/80 °C	85	–
Br(CH ₂) ₂ Br	6.2.20.B/1 h/rt	–	69 ^{a,f}
<i>With 2-ethoxycarbonylcyclohexanone</i>			
EtBr	6.2.20.F/20 min/rt	96	–
<i>n</i> -BuBr	6.2.20.F/30 min/rt	93	–
<i>n</i> -C ₆ H ₁₃ Br	6.2.20.F/30 min/80 °C	83	–
<i>With CH₂(CN)CO₂Me</i>			
MeI	6.2.20.A/10 min/rt	48.5	25.5
EtI	6.2.20.A/20 min/rt	72	14
<i>n</i> -BuI	6.2.20.A/1 h/rt	86	7
<i>With CH₂(CN)CO₂Et</i>			
PhCH ₂ Cl	6.2.20.D/3 h/90 °C	–	87
Br(CH ₂) ₂ Br	6.2.20.B/1 h/rt	–	86 ^{a,e}
<i>With CH₂(CN)₂</i>			
PhCH ₂ Br	6.2.20.E/4 h/40 °C	40	18
Br(CH ₂) ₂ Br	6.2.20.B/1 h/rt	–	49 ^{a,e}

^a Isolated as mono acid. ^b + 23.5% *O*-alkylated product. ^c Power level 6. ^d Power level 2. ^e Cyclic product.

mixture is extracted with CH₂Cl₂ (200 ml) and the extract is evaporated to yield the alkylated product.

Method H (with microwave irradiation): An intimate mixture of the β -keto ester. (5 mmol), the alkylating agent (5 mmol), KOH:K₂CO₃ (1 : 4, 4 g), and TBA-Cl (0.15 g, 0.5 mmol) is irradiated in a 650 W microwave oven. When the reaction is complete, Et₂O (50 ml) is added to the cooled solid, the suspension is filtered, and the ethereal filtrate is evaporated to yield the alkylated product.

6.2.21 Reaction of glycopyranosyl halides with activated methylene groups

The glycosyl halide (1.5 mmol), β -dicarbonyl compound (2 mmol), anhydrous K₃PO₄ (0.85 g) and TBA-Br (24 mg, 0.075 mmol) in MeCN (10 ml) are stirred at room temperature. When the reaction is complete, as indicated by TLC analysis, the mixture is filtered and evaporated to yield the C-glycosyl derivative.

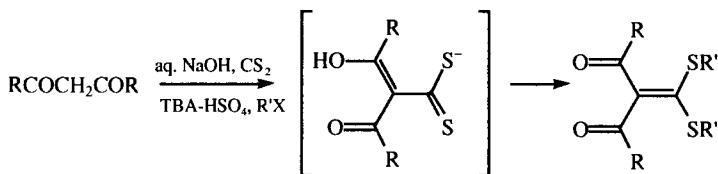
6.2.22 Alkylation of nitroacetic esters

Method A: The alkylating agent (10.5 mmol) is added with stirring to $\text{O}_2\text{NCH}_2\text{CO}_2\text{Me}$ (1.2 g, 10 mmol) in DMF (10 ml) followed by TEBA-Cl (9 mg, 0.04 mmol) and KHCO_3 (5 g) at room temperature and the mixture is then heated at 60°C for ca. 16 h. The solvent is removed under reduced pressure and H_2O (50 ml) is added to the residue. The aqueous mixture is extracted with Et_2O (3×30 ml) and the dried extracts are evaporated to yield the alkylated product (~70%).

Method B (in the absence of a solvent): The alkylating agent (1 mmol), $\text{O}_2\text{NCH}_2\text{CO}_2\text{Et}$ (0.27 g, 2 mmol) and TBA-Br (26 mg, 0.08 mmol) are stirred for 30 min and KHCO_3 (0.1 g) is then added. The mixture is stirred for a further 24–72 h at room temperature and then extracted with CH_2Cl_2 (30 ml). The extract is evaporated and the crude product is purified by chromatography from silica (e.g. using PhCH_2Br , 24 h, 58%; $\text{CH}_2=\text{CHCH}_2\text{Br}$, 36 h, 40%; $\text{BrCH}_2\text{CO}_2\text{Et}$, 72 h, 44%).

Method C: The ester (0.2 mol) in CH_2Cl_2 (75 ml) is passed repeatedly (7–8 times) through a column of Amberlite IRA 400 (OH^- form) (50 g). The column is washed with CH_2Cl_2 (25 ml) and the combined solutions are evaporated to dryness under reduced pressure. The resin (8 g) is then refluxed with the alkylating agent (9.2 mol) in CH_2Cl_2 (40 ml). On completion of the reaction, the resin is collected, washed with CH_2Cl_2 (25 ml) and dilute HCl (15 ml). The acid solution is extracted with CH_2Cl_2 (15 ml) and the combined organic solutions are dried (Na_2SO_4) and evaporated to give the alkylated product [56% with MeI after 32 h; 45%, PhCH_2Br , 24 h; 54%, $\text{BrCH}_2\text{CO}_2\text{Me}$, 27 h; 70%, $\text{Br}(\text{CH}_2)_2\text{CO}_2\text{Me}$, 45 h].

Carbon disulphide should not be used as the solvent for alkylation of β -diketones, as the carbanion reacts preferentially with the solvent to generate the dithiocarboxylate derivative, which undergoes mono- and dialkylation (Scheme 6.9) [95]. Ketene thioacetals have also been isolated from acetophenones (60–80%) and cyclopentadiene (80%) using an ultrasound technique in carbon disulphide [96] and, in a similar manner, pyrazol-5-ones form pyrazole-4-dithiocarboxylic esters [97].



Scheme 6.9

6.2.23 Ketene dithioacetals

The β -diketone (50 mmol) and TBA- HSO_4 (34 mg, 0.1 mmol) in CS_2 (50 ml) are stirred with aqueous NaOH (8%, 100 ml) at room temperature for 10 min. The haloalkane (0.15 mol) is added and the mixture stirred for a further 1 h. The organic phase is separated, dried (MgSO_4), and evaporated to yield the ketene dithioacetal.

Confusing reports come for the alkylation of malonic esters [e.g. 98, 99]. Early studies indicated that monoalkylation occurred to the exclusion of dialkylation and that, under vigorous reaction conditions, the ester groups (particularly with methyl esters) were hydrolysed concomitant with the dialkylation. Use of the di-*t*-butyl esters obviated the problem of hydrolysis [100]. Cyanoacetic esters and malonodinitrile also are hydrolysed during liquid:liquid phase-transfer catalysed alkylation to yield alkylated cyanoacetic acids [75]. *O,S*-Diethyl thiomalonate has been dialkylated successfully with two different alkylating agents without hydrolysis of the ester groups in a two-stage liquid:liquid reaction [101].

Mildly basic liquid:liquid conditions with a stoichiometric amount of catalyst prevent hydrolysis during alkylation [101] and, more recently, it has been established that solid-liquid or microwave promoted reactions of 'dry' materials are more effective for monoalkylation [102–106] of the esters and also permits dialkylation without hydrolysis. Solid:liquid phase-transfer catalytic conditions using potassium *t*-butoxide have been used successfully for the *C*-alkylation of diethyl acetamidomalonate and provides a convenient route to α -amino acids [105, 107]; use of potassium hydroxide results in the *trans*-esterification of the malonate, resulting from hydrolysis followed by *O*-alkylation. The rate of *C*-alkylation of malonic esters under solid:liquid phase-transfer catalytic conditions may be enhanced by the addition of 18-crown-6 to the system. The overall rate is greater than the sum of the individual rates observed for the ammonium salt or the crown ether [108].

Reaction of malonic esters with 1,2-dibromoethane and 1,3-dibromopropane under liquid:liquid two-phase conditions produces the cyclopropane- and cyclobutane-1,1-dicarboxylic esters, which can be hydrolysed under the basic conditions (6.2.24.C) [e.g. 75, 109] and decarboxylated to give the monocarboxylic acid [e.g. 109].

Diethyl malonate reacts with iodine under basic solid:liquid conditions (procedure 6.4.20 omitting the alkene) to produce tetraethyl ethane-1,1,2,2-tetracarboxylate (Scheme 6.28) [110]; the ethenetetracarboxylate is also formed, presumably from the reaction of the initially formed iodomalonnate with its carbanion and subsequent elimination of hydrogen iodide.

6.2.24 Alkylation of malonic esters (Table 6.10)

Method A (monoalkylation and two-step dialkylation): TBA- H_2SO_4 (3.4 g, 10 mmol) and NaOH (0.8 g) in H_2O (10 ml) are added with stirring to the ester (10 mmol) and the first alkylating agent (20 mmol) in CH_2Cl_2 (10 ml) at 10°C . The mixture is stirred until the aqueous phase is neutral (*ca.* 30 min). The organic phase is separated and the aqueous phase is extracted with CH_2Cl_2 (2×10 ml). The combined organic solutions are evaporated and the residue is extracted with Et_2O (25 ml). Evaporation of the filtered ethereal solution yields the monoalkylated ester. Further alkylation with a second alkylating agent can be achieved by repeating the procedure.

Method B: $\text{CH}_2(\text{CO}_2\text{Et})_2$ (16 g, 0.1 mol) and the alkylating agent (0.2–0.3 mol) are added with stirring to aqueous NaOH (37%, 200 ml) and TEBA-Cl (22.3 g, 0.1 mol). The mixture is stirred at room temperature for 16 h and then diluted with H_2O (200 ml) and

TABLE 6.10
Selected examples of the alkylation of malonic esters

Haloalkane	Reaction conditions	% yield	
		Monoalkylation	Dialkylation
<i>With CH₂(CO₂Et)₂</i>			
MeI	6.2.24.A/30 min/rt	86	3
	6.2.24.A ^d /30 min/rt	4	96
	6.2.24.B/16 h/rt	—	82
EtI	6.2.24.A/30 min/rt	88	—
EtBr	6.2.24.D/1 h/110 °C	93	—
<i>n</i> -PrBr	6.2.24.A/30 min/rt	45	—
	6.2.24.B/16 h/rt	42	47
<i>n</i> -BuBr ^b	6.2.24.E/2 min	86	—
<i>n</i> -BuI	6.2.24.A/30 min/rt	85	—
CH ₂ =CHCH ₂ Br ^c	6.2.24.E/2 min	75	—
	6.2.24.B/16 h/rt	—	83
ClCH=CHCH ₂ Cl	6.2.24.B/1 h/0 °C	—	59
HC≡CCH ₂ Br	6.2.24.B/16 h/rt	90	—
PhCH ₂ Cl ^d	6.2.24.E/2 min	72	—
	6.2.24.B/1.5 h/rt	—	82
4-MeOC ₆ H ₄ CH ₂ Cl ^d	6.2.24.E/2 min	71	—
4-ClC ₆ H ₄ CH ₂ Cl ^b	6.2.24.E/2 min	—	64
Br(CH ₂) ₂ Br	6.2.24.D/12 h/80 °C	—	85 ^e
Br(CH ₂) ₃ Br	6.2.24.C/1 h/rt	—	23
<i>With RCH(CO₂Et)COSEt</i>			
CH ₂ Br ₂	6.2.24.A/1.5 h/10	63 ^f	—
<i>With CH₂(CO₂<i>t</i>-Bu)₂</i>			
<i>n</i> -BuBr	—	—	39
CH ₂ =CHCH ₂ Cl	—	96	—
PhCH ₂ Cl	—	53.5	16
Br(CH ₂) _{<i>n</i>} Br (<i>n</i> = 2)	—	—	90
(<i>n</i> = 4)	—	75	—
<i>With MeCONHCH(CO₂Et)₂</i>			
<i>n</i> -C ₈ H ₁₇ Br	6.2.24.D	53	—
<i>n</i> -C ₁₆ H ₃₃ Br	6.2.24.D	87	—

^a 30 mmol TBA-HSO₄, ^b 25 mmol, ^c 20 mmol, ^d 11 mmol, ^e using K₂CO₃ and TBA-Br. 75% of alkylated diacid using 6.2.24.C, ^f BrCH₂CR(CO₂Et)COSEt.

extracted with Et₂O (2 × 100 ml). The combined extracts are washed with H₂O (3 × 100 ml) and brine (100 ml), dried (MgSO₄), and evaporated to yield the dialkylated malonic ester.

Method C: The malonic ester (15 mmol) is stirred with aqueous NaOH (50%, 30 ml) and TEBA-Cl (3.54 g, 15 mmol). The alkylating agent (0.25 mmol) is then added and the mixture is stirred for 1 h at room temperature. The mixture is diluted with H₂O (75 ml) and extracted with Et₂O (3 × 25 ml). The dried (MgSO₄) extracts are evaporated to give the alkylated ester. Acidification of the aqueous phase with conc. HCl and extraction with Et₂O (3 × 25 ml) yields the alkylated malonic acid or *t*-butyl ester.

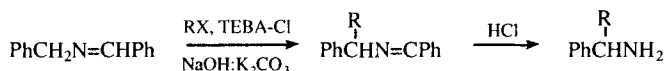
Method D (solid:liquid process): The malonate (10 mmol), alkylating agent (10 mmol), *t*-BuOK (1.12 g) and Aliquat (0.2 g, 0.5 mmol) are stirred for 3 h at 70°C and then extracted with Et₂O (3 × 5 ml). The extracts are washed with aqueous HCl (1M, 2 × 20 ml) and evaporated to yield the alkylated product.

Method E (microwave reaction): An intimate mixture of CH₂(CO₂Et)₂ (1.62 g, 10 mmol), the alkylating agent (10–25 mmol), TBA-Br (0.32 g, 1 mmol), and anhydrous K₂CO₃ (5.48 g, 40 mmol) is irradiated in a 650 W microwave oven for 2 min. Et₂O (50 ml) is added, and the mixture is filtered and evaporated to yield the alkylated malonate.

The greater CH acidity of Meldrum's acid (*pK_a* 4.97), compared with the malonic esters, results in a more rapid mono- and dialkylation. Concomitant hydrolytic ring opening may occur under liquid:liquid two-phase conditions and yields of the monoalkylated product tend to be low (30–40%) [111], but the ring is retained under non-aqueous solid:liquid two-phase conditions [112, 113]. Further alkylation of the monoalkylated derivatives with a second (different) alkylating agent is possible [112, 113].

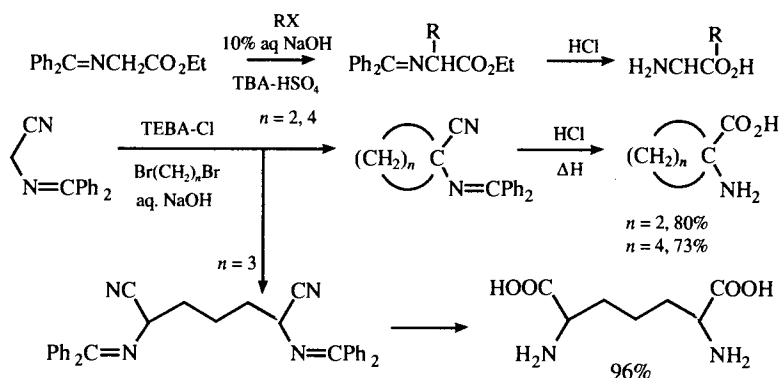
6.2.25 Alkylation of Meldrum's acid

Powdered anhydrous K₂CO₃ (4.15 g, 30 mmol) and TEBA-Cl (6.83 g, 30 mmol) are added to Meldrum's acid (1.44 g, 10 mmol) in CHCl₃ or MeCN (15 ml) and the mixture is stirred while the alkylating agent (15 mmol for monoalkylation; 30 mmol for dialkylation) in CHCl₃ (15 ml) is added. The mixture is stirred at 50–60°C for a further 4–8 h and H₂O (20 ml) is then added. The aqueous phase is separated and extracted with CHCl₃ (2 × 20 ml). The combined organic solutions are dried and evaporated. H₂O (20 ml) and Et₂O (20 ml) are added to the residue and the ethereal phase is washed with H₂O (15 ml), dried (MgSO₄), and evaporated to give the alkylated product (86% dialkylated product from MeI after 4 h; 90%, EtI, 6 h; 85%, *n*-BuI, 8 h; 94%, PhCH₂Cl, 2.5 h; 76%, BrCH₂CO₂Et, 3 h; 86%, PhCOCH₂Br, 2.5 h).



Scheme 6.10

N-Benzylimines and related systems have been C-alkylated under solid:liquid two-phase conditions (Scheme 6.10) [114–116]; under liquid:liquid conditions, there is virtually no reaction. The corresponding alkylation of the more reactive imino nitriles [117, 118] and imino acetic esters [119–124] provides a route to α-amino acids. Liquid:liquid and solid:liquid two-phase conditions have been used and, in combination with microwave irradiation, reaction times have been reduced significantly [125]. Reaction with α,ω-dibromoalkanes can produce either cyclic or acyclic products depending on the chain length (Scheme 6.11). It has been claimed that monoalkylation using potassium hydrogen carbonate under solid:liquid two-phase conditions does not always require the catalyst, and that the use of solid potassium hydroxide with the ammonium catalyst and two equivalents of the alkylating agent leads to the formation of the dialkylated products [124].



Scheme 6.11

6.2.26 Mono-C-alkylation of $\text{ArCH}_2\text{N}=\text{CHPh}$

The alkylating agent (20 mmol) is added with stirring to the imine (10 mmol), TEBA-Cl (0.23 g, 1 mmol) and powdered NaOH (1.6 g) and K_2CO_3 (2.76 g) in MeCN (20 ml). The mixture is stirred at room temperature. On completion of the reaction, the mixture is filtered and the solid is washed with PhH (100 ml). The combined organic solutions are evaporated under reduced pressure and EtOAc (25 ml) is added to the residue. The suspension is filtered and the filtrate is evaporated to yield the product (Ar = Ph: 72% with EtBr after 18 h; 71%, *i*-PrBr, 15 h; 80%, *n*-BuBr, 18 h; 71%, cyclo- $\text{C}_6\text{H}_{11}\text{Br}$, 48 h; 73%, PhCH_2Cl + 10% dialkylated product, 15 h; 65%, PhCH_2Br , 48 h; 52%, $\text{CH}_2=\text{CHCH}_2\text{Cl}$ + 13% dialkylated product, 15 h; 75%, $\text{CH}_2=\text{CHCH}_2\text{Br}$, 42 h). Hydrolysis of the imine with HCl gives the amine.

6.2.27 Mono-C-alkylation of imino nitriles and esters (Table 6.11)

Method A (liquid:liquid conditions): The alkylating agent (27.3 mmol) is added dropwise to aqueous NaOH (50%, 15 ml), the imino nitrile (22.7 mmol) and TEBA-Cl (0.5 g, 2.2 mmol) in PhMe (5 ml) at 0°C . The mixture is stirred at room temperature for 24 h and PhMe (100 ml) and H_2O (100 ml) are then added. The aqueous phase is separated and extracted with PhMe (3×50 ml). The combined organic solutions are washed with H_2O (50 ml) and brine (50 ml), dried (MgSO_4), and evaporated under reduced pressure at $<60^\circ\text{C}$ to yield the alkylated product.

Method B (liquid:liquid conditions): The alkylating agent (4.8 mmol) is added dropwise to aqueous NaOH (10%, 5 ml), the imino ester (4 mmol) and TBA- HSO_4 (0.14 g, 0.4 mmol) in CH_2Cl_2 (5 ml) and the mixture is stirred at room temperature overnight. The organic phase is separated, washed with H_2O (10 ml) and brine (10 ml), dried (MgSO_4), and evaporated. The residue is extracted with Et_2O (2×15 ml), and the ethereal solutions are evaporated and the alkylated imino ester is purified by chromatography.

Method C (solid:liquid conditions): The alkylating agent (27.3 mmol) in MeCN (5 ml) is added to the imino nitrile (22.7 mmol), TBA-Br (0.7 g, 2.2 mmol) and powdered K_2CO_3 (18.8 g, 136 mmol) in refluxing MeCN (25 ml). The mixture is refluxed and stirred for 12 h and then worked up as described in 6.2.27.A.

TABLE 6.11
Selected examples of the alkylation of imino nitriles and imino esters

Alkylating agent	Method	% yield of $\text{Ph}_2\text{C}=\text{NCHRCN}$	Method	% yield of $\text{Ph}_2\text{C}=\text{NCHRCO}_2\text{Et}$
Me_2SO_4	6.2.27.A	95		
MeI			6.2.27.B	89
EtBr	6.2.27.A	90	6.2.27.B	77
<i>i</i> -PrBr	6.2.27.A	79	6.2.27.B	60
PhCH_2Cl	6.2.27.A	60 ^a	6.2.27.B	78

^a 75% when 30% aq NaOH used.

C-Alkylation of 2-oxazolin-5-ones under catalysed mildly basic conditions provides a convenient route to α -branched α -amino acids (50–80%) [126]. Similarly, *N*-alkyloxindoles are mono- and di-alkylated at the 3-position [127]. For other examples of the alkylation of heteroaryl systems, see Chapter 5.

6.2.28 Alkylation of 2-phenyl-2-oxazolin-5-ones

Na_2CO_3 (1.5 g) in H_2O (11 ml) is added to the oxazolinone (5 mmol) and TBA-Br (165 mg, 0.5 mmol) in CH_2Cl_2 (15 ml), followed by the alkylating agent (5 mmol). The mixture is stirred at room temperature until the reaction is complete and the aqueous phase is then separated and extracted with CH_2Cl_2 (10 ml). The combined organic solutions are washed with H_2O until neutral, dried (Na_2SO_4), and evaporated to yield the 4-alkylated derivative (2,4-diphenyl-2-oxazolin-5-one with MeI, 75 min, 65%; EtI, 3 h, 52%; PhCH_2Cl , 2 h, 61%; $\text{CH}_2=\text{CHCH}_2\text{Br}$, 15 min, 77%; $\text{HC}\equiv\text{CCH}_2\text{Br}$, 10 min, 57%; PhCOCH_2Br , 1.5 h, 80%).

The phase-transfer catalysed alkylation of *S*-cyanomethyl dithiocarbamates provides a high yielding and convenient route to aldehydes (from monoalkylation) and ketones (from dialkylation) [128]. The procedure has been used to produce a range of alicyclic and small-ring ketones (>85%).

Highly acidic triply-activated methylene groups are readily alkylated under mildly basic conditions, e.g. dicyanoacetic esters are converted into the quaternary ammonium salts, which give the 2,2-dicyanopropionic esters upon reaction with iodomethane [129].

6.2.29 2,2-Dicyanopropionic esters

TEBA-Cl (9.12 g, 40 mmol) and aqueous NaOH (0.4 M, 100 ml) are added to the dicyanoacetic ester (40 mmol) and the mixture is stirred for 5 min at room temperature. The aqueous solution is extracted with CHCl_3 (2 \times 100 ml) and the extracts are dried (MgSO_4) and evaporated. The residue is taken up in EtOH (70 ml). Et_2O (150 ml) is added and the solution cooled to 0°C to yield the TEBA salt of the ester.

The salt (30 mmol) and MeI (2.81 ml, 45 mmol) in CHCl_3 (60 ml) are stirred at room temperature for 72 h. The solution is evaporated and the residue triturated with Et_2O

(150 ml). Evaporation of the filtered solution yields the propionic ester (methyl ester, 62%; *n*-butyl ester, 42%; *i*-butyl ester, 56%; 2-ethylhexyl ester, 57%; phenyl ester, 58%).

Sonication [130, 131] aids the standard phase-transfer catalysed [e.g. 132, 133] C-alkylation of Reissert compounds. As much as twofold increases in yield are observed with shortened reaction times. No alkylation is observed when sonication is used alone.

6.2.30 C-Alkylation of Reissert compounds

Method A (normal conditions): The Reissert compound (8.6 mmol), alkylating agent (9 mmol) and quaternary ammonium salt (1 mmol) in PhH (20 ml) is stirred with aqueous NaOH (50%, 5 ml) for 13 h at room temperature. The mixture is adjusted to pH 6 with aqueous H₂SO₄ (5%) and the organic phase is separated, dried (MgSO₄), and evaporated to yield the alkylated Reissert compound.

Method B (with sonication): Sonication of the Reissert compound (4.6 mmol), haloalkane (6.6 mmol), and TEBA-Cl (34 mg, 0.15 mmol) in CH₂Cl₂ (2.5 ml) and aqueous NaOH (50%, 1.8 ml) is conducted for 20 min. Work-up at this stage, as described in 6.2.30.A, yields the alkylated Reissert compound. Addition of EtOH (6 ml) and sonication for a further 30 min with subsequent work-up by addition of the mixture to H₂O (20 ml) and extraction with CH₂Cl₂ (3 × 10 ml) produces the C-alkylated heteroarene, which is isolated as the hydrochloride salt (70–90%) by saturation of the dried organic extracts with HCl gas.

6.2.31 Hydroxymethylheteroarenes

The Reissert compound (5.7 mmol), an aryl aldehyde and TEBA-Cl (14 mg, 0.06 mmol) in CH₂Cl₂ (3 ml) are sonicated with aqueous NaOH (50%, 2.5 ml) for 5 min. EtOH (8 ml) and CH₂Cl₂ (15 ml) are added and sonication is continued for a further 85 min and the mixture is then poured into H₂O (20 ml). The aqueous phase is separated and extracted with CH₂Cl₂ (3 × 10 ml). The combined organic solutions are dried (MgSO₄), concentrated to 20 ml, and saturated with HCl gas to yield the hydroxymethylheteroarene hydrochloride (80–99%).

C-Alkylation of weakly activated methylpyridines to yield the isopropyl and *tert*-butyl derivatives (35–40%), which normally requires the use of strong bases, such as alkylolithiums, is carried out effectively using a phase-transfer catalyst and aqueous sodium hydroxide on the *N*-methylpyridinium salts. The pyridines are regenerated by reaction with sodium acetate or sodium 4-toluenethiolate [134]. 3-Methylpyridine fails to react under these conditions and the synthesis of 2-ethylpyridines by this procedure is also unsuccessful.

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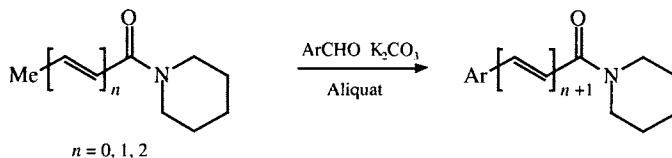
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6.3 ALDOL AND RELATED REACTIONS

Simple aldol condensation products have been obtained in high yield under solid:liquid phase-transfer catalytic conditions from, for example, aryl aldehydes and *n*-propanal or *n*-heptanal [see, e.g. 1, 2]. Similarly, certain aryl aldehydes and pivaldehyde react with *N*-crotonyl and *N*-sorbyl piperidides to produce the conjugated aldol derivatives (87–97%) (Scheme 6.12) [3]. The reaction is, however, rather selective as it not only fails with 2-nitrobenzaldehyde but also with π -excessive aryl aldehydes, and the base-catalysed synthesis of piperine from *N*-crotonylpiperidine and piperonal in dimethylsulphoxide, catalysed by benzyltriethylammonium chloride, occurs in high yield (80%) [4]. The micelle-catalysed procedure [5], using cetyltrimethylammonium chloride, for the condensation of aryl aldehydes with enolizable alkyl ketones requires significantly less base than does the conventional phase-transfer catalysed reactions in which enolizable aliphatic aldehydes and ketones self-condense to produce polymers [3]. Microwave irradiation has a significant effect upon the reaction time (from 3 days to 1 minute) of the solid:liquid two-phase aldol condensation of aryl aldehydes with aliphatic aldehydes without prejudicing the yields (82%) [6]. Formaldehyde and 2-arylalkanoates produce 2-hydroxymethyl derivatives solid:liquid two-phase conditions [7].

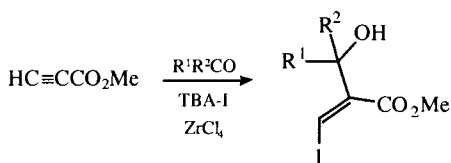


Scheme 6.12

6.3.1 Micelle-catalysed synthesis of chalcones and related compounds

The aryl aldehyde (10 mmol) and the methyl ketone (10 mmol) are stirred at room temperature with aqueous NaOH (0.02 M, 100 ml) and CTMA-Br (50 mg, 1.37 mmol). When the reaction is complete, as shown by TLC analysis, the mixture is extracted with $E_2O:n\text{-C}_6\text{H}_{14}$ (1:1, 3×35 ml). The dried (MgSO_4) extracts are evaporated to yield the aldol condensation product [e.g. from MeCOPh : 74% with PhCHO ; 78%, 4- $\text{MeOC}_6\text{H}_4\text{CHO}$; 95%, 4- $\text{ClC}_6\text{H}_4\text{CHO}$; 90%, 4- $\text{Me}_2\text{NC}_6\text{H}_4\text{CHO}$. PhCHO and Me_2CO produce $(\text{PhCH}=\text{CH})_2\text{CO}$ (89%)].

Zirconium tetrachloride promotes a tandem nucleophilic addition and aldol-type condensation reaction of methyl propynoate, or *N,N*-dimethylpropynamide, with aldehydes, or ketones, in the presence of tetra-*n*-butylammonium iodide (Scheme 6.13) [8] with a high selectivity towards the formation of *Z*-isomers. A similar reaction occurs between aliphatic and aromatic aldehydes and penta-3,4-dien-2-one to yield 1-substituted 2-acetyl-3-iodobut-3-enols (50–75%) [9].



Scheme 6.13

6.3.2 2-(1-Hydroxyalkyl)-3-iodopropenoates

ZrCl₄ (0.28 g, 1.2 mmol) is added to HC≡CCO₂Me (84 mg, 1 mmol), the aldehyde or ketone (1.2 mmol) and TBA-I (0.4 g, 1.1 mmol) in CH₂Cl₂ (5 ml) at 0°C. The mixture is stirred at 0°C for *ca.* 5 h under N₂ and when the reaction is complete, as shown by TLC analysis, H₂O (5 ml) is added and the total mixture is extracted with CH₂Cl₂ (3 × 5 ml). The combined extracts are dried (MgSO₄) and evaporated to give the ester [R¹, R², % yield: *n*-Pr, H, 70%; *i*-Pr, H, 83%, *t*-Bu, H, 90%; Ph, H, 87%; Ph, Me, 60%; (CH₃)₄, 32%].

O-Silylated enols undergo aldol condensations with aryl aldehydes in good yield, when catalysed by tetra-*n*-butylammonium fluoride (*cf.* alkylation reactions) [10]. In stoichiometric amounts the same catalyst promotes the self condensation of enolizable ketones [e.g. 11]. Tetra-*n*-butylammonium triphenyldifluorosilicate is a better agent to generate carbanions from trimethylsilyl compounds [12] and, with this catalyst, benzaldehyde reacts with a range of carbanions to form the carbinols. Ketones and aldehydes react with benzyltrimethylsilane and with trifluoromethyltrimethylsilane to form 1-phenyl- and 1,1,1-trifluoroalkan-2-ols, respectively, in high yield [13, 14], whereas lactones undergo ring-opening after the initial nucleophilic attack by the trifluoromethyl anion to yield ω-hydroxyl-1,1,1-trifluoroalkan-2-ones [15].

6.3.3 Fluoride-catalysed aldol condensation of silyl enol ethers

The aryl aldehyde (1.1 mmol) and trimethylsilyl enol ether (1 mmol) are added sequentially to TBA-F (16 mg, 0.06 mmol) in THF (2 ml) at -78°C. The mixture is stirred at -78°C for 3–5 h, then warmed to room temperature, and H₂O (25 ml) is added. The aqueous mixture is extracted with Et₂O (3 × 15 ml) and the dried (MgSO₄) extracts are fractionally distilled to yield the aldol product (e.g. from PhCHO and 1-trimethylsilyloxycyclohexene, 84%, 6-methyl-1-trimethylsilyloxycyclohexene, 68%; 1-trimethylsilyloxycycloheptene, 80%, 3-trimethylsilyloxypent-2-ene, 70%].

6.3.4 Reaction of carbonyl compounds with fluoride-generated carbanions

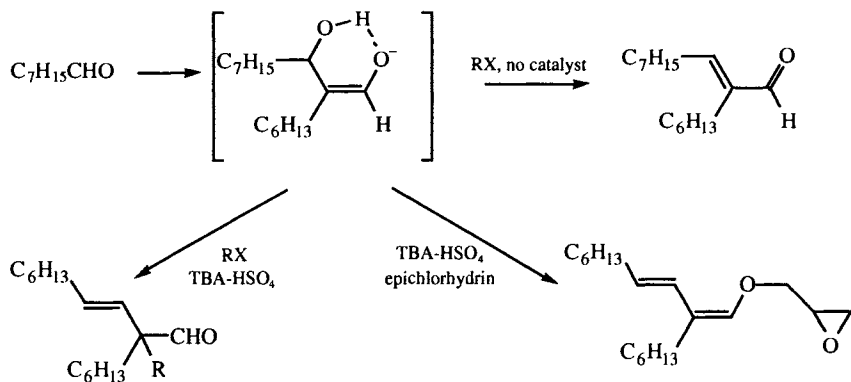
TBA-F·3H₂O (20 mg, 0.063 mmol) is added to the carbonyl compound (10 mmol) and the trimethylsilyl compound (12 mmol) in THF (25 ml) at 0°C. The mixture is allowed to come to room temperature and is stirred until the reaction is complete (*ca.* 1 h), as shown by GLC analysis. Aqueous HCl (1 M, 5 ml) is added and the mixture is stirred until all of the silane has been hydrolysed (1–15 h). The aqueous mixture is extracted with Et₂O

(2 × 50 ml) and the ethereal extracts are washed with H₂O (50 ml) and brine (50 ml), dried (MgSO₄), and evaporated to yield the trifluoroalkanol [e.g. *n*-Bu₂C(OH)CF₃, 87%; *n*-C₆H₁₃CH(OH)CF₃, 74%; PhC(CF₃)(OH)Me, 74%; Ph₂C(OH)CF₃, 88%; PhCH(OH)CH₂Ph, 92%; Ph₂C(OH)CH₂Ph, 85%; PhCH=CHCH(OH)CH₂Ph, 85%; PhC(OH)(Me)CH₂Ph, 75%; Me₂C(OH)CH₂Ph, 61%].

6.3.5 Aldol-type condensation of carbanions generated by tetra-*n*-butylammonium triphenyldifluorosilicate

PhCHO (1 mmol), the trimethylsilyl compound (2 mmol), and TBA-Ph₃SiF₂ (54 mg, 0.1 mmol) are heated to 70 °C in THF (5 ml) under N₂. Volatile material is removed under reduced pressure and the residue is dissolved in Et₂O (30 ml). The extract is stirred with aqueous HCl (1 M, 30 ml) until all of the trimethylsilane is hydrolysed, as shown by GLC analysis, and then washed with H₂O (30 ml) and aqueous NaHCO₃ (5%, 30 ml), dried (MgSO₄), and evaporated to yield the carbinol [e.g. PhCH(OH)C≡CPh, 81% at 0 °C; PhCH(OH)CH₂CH=CH₂, 92%; PhCH(OH)CH₂Ph, 93%].

It has been noted that when the aldol condensation is conducted on simple aliphatic aldehydes, such as octanal, in the presence of an alkylating agent and a quaternary ammonium salt the 2-position is alkylated and the alk-3-enal is isolated (Scheme 6.14) [16]. In the absence of the quaternary ammonium salt, the normal aldol adduct is formed with no alkylation. It is noteworthy that in the presence of epichlorhydrin the dienyl ether is formed.



Scheme 6.14

Unlike the corresponding reaction of β -keto esters with α,β -unsaturated aldehydes, which produce Michael adducts, α -cyanoacetic esters undergo the aldol reaction forming α -cyanodienoic esters [17].

6.3.6 Ethyl 2-cyano-2,4-dienoates

The α,β -unsaturated aldehyde (50 mmol) is added to the α -cyanoacetic ester (50 mmol), K₂CO₃ or Na₂CO₃ (50 mmol) and TEBA-Cl (0.23 g, 1 mmol) in PhH (20 ml). The

mixture is stirred at room temperature until the reaction is complete and then filtered. The filtrate is added to Et₂O (50 ml), dried (MgSO₄), and fractionally distilled to yield the dienoate.

Methyl methylthiomethyl sulfoxide reacts with a range of aryl aldehydes under the influence of Triton B to produce aldol-type adducts with the *E*-configuration, which are solvolysed in alcoholic hydrochloric acid to produce arylacetic esters [18, 19]; the reaction fails with aryl ketones [20]. Sulphones generally give high yields (>85%) of the aldol products with aryl aldehydes under liquid:liquid two-phase catalysed conditions [e.g. 21–23], although dimethylsulphone reacts with benzaldehyde to form 3,5-diphenyl-1,4-thiadioxane-*S,S*-dioxide (60%) using procedure 6.3.8 [24]. In all cases, no Cannizzaro products are formed whereas, in contrast, the Cannizzaro reaction is prevalent when crown ethers are used as phase-transfer catalysts [24].

6.3.7 Condensation of aryl aldehydes with methyl methylthiomethyl sulfoxide

MeSCH₂SOMe (1.17 g, 9.4 mmol) and the aryl aldehyde (9.4 mmol) in THF (10 ml) are refluxed with Triton-B (40% in MeOH, 1.2 ml) for 4 h. CH₂Cl₂ (100 ml) is then added and the solution is washed with sulphuric acid (0.5 M, 20 ml) and H₂O (2 × 50 ml), dried (Na₂SO₄), and evaporated to yield the phenylethene (e.g. from *i*-PrCHO, 68%; PhCHO, 88%; 4-MeOC₆H₄CHO, 82%; 3-PhOC₆H₄CHO, 61%; 2-BrC₆H₄CHO, 51%; 2-thienylCHO, 86%).

6.3.8 Condensation of aryl aldehydes with sulphones

The sulphone (10 mmol) and TEBA-Cl (0.45 g, 2 mmol) in CH₂Cl₂ (20 ml) are stirred with aqueous NaOH (50%, 20 ml) for 15 min at room temperature. The aryl aldehyde (30 mmol) in CH₂Cl₂ (5 ml) is then added dropwise and the mixture is stirred for a further 2–6 h at room temperature. On completion of the reaction, the mixture is poured into H₂O (50 ml) and extracted with Et₂O (3 × 50 ml). The organic solutions are washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the α,β-unsaturated sulphone (e.g. from PhSO₂Me and PhCHO, 86%; 2-naphthylCHO, 85%).

The Darzens reaction between aldehydes and ketones with activated halomethyl compounds is an effective route to oxiranes under phase-transfer catalytic conditions and the catalyst has a profound stereochemical control of the substituents (see Chapter 12). The reaction has been conducted in high yield under liquid:liquid and solid:liquid two-phase conditions with a range of halomethyl compounds [e.g. 25–30]. Ketones tend to be much slower in their reaction and benzylic ketones undergo alkylation with chloroacetonitrile in preference to the Darzens reaction [25].

The oxiranes obtained from the reaction of chloromethylsulphones with aldehydes and ketones can be isolated [26, 27], but tend to be unstable in the basic media. Rearrangement of the toluenesulphonyloxiranes produces the sulphonyl aldehydes (Scheme 6.15) [26]. When chiral chloromethylsulphonamides are used, asymmetric

induction is observed to yield optically active oxiranes; maximum induction occurs with (–)-2-methoxymethyl-*N*-(chloromethyl-sulphonyl)pyrrolidine (ee ~50%) [31].



Scheme 6.15

6.3.9 Darzens reaction

Method A: The chloromethyl compound (35 mmol) and aldehyde (25 mmol) are added with stirring to K_2CO_3 (6.9 g) and TEBA-Cl (0.285 g, 1.25 mmol) in DMF (8 ml) under N_2 at 40°C . When the reaction is complete, as indicated by GLC analysis, the mixture is poured into H_2O (50 ml) and extracted with Et_2O (2×50 ml). The extracts are washed well with H_2O , dried (Na_2SO_4), and evaporated to yield the oxirane.

Method B: The chloromethyl compound (15 mmol) and aldehyde or ketone (18 mmol) in MeCN (2 ml) are added with stirring to TEBA-Cl or TBA-Cl (0.22 mmol) in aqueous NaOH (50%, 10 ml) and the mixture is stirred at $30\text{--}35^\circ\text{C}$ for ca. 45 min. The oxirane is isolated by a procedure analogous to that described in 6.3.9.A.

Method C: The α -chlorophenylacetonitrile, prepared *in situ* from PhCH_2CN (20 mmol) and TEBA-Cl (50 mg, 0.22 mmol) in CCl_4 (15 ml) and aqueous NaOH (50%, 10 ml), is stirred with the aldehyde (25 mmol) at $15\text{--}20^\circ\text{C}$ for ca. 15 min. The mixture is diluted with H_2O (50 ml) and extracted with PhH (2×25 ml). Evaporation and fractional distillation yields the oxirane.

The reaction of trimethylsulphonium iodide [32], or polymer-supported sulphonium salts [33], with aldehydes and ketones produces oxiranes under relatively mild

TABLE 6.12
Selected examples of the Darzens reaction

Aldehyde	Halo compound	Reaction conditions	% yield
PhCHO	$\text{ClCH}_2\text{CO}_2\text{Et}$	6.3.9.A/ 40°C /40 h	90
	$\text{MeCHClCO}_2\text{Me}$	6.3.9.A/ 40°C /24 h	85
	$\text{PhCHClCO}_2\text{Et}$	6.3.9.A/ 20°C /45 h	85
	ClCH_2CN	6.3.9.C/ 20°C	75
	PhCHClCN	6.3.9.C/ 20°C /15 min	65
	$\text{ToISO}_2\text{CH}_2\text{Br}$	6.3.9.B/ 35°C /45 min	60
<i>i</i> -PrCHO	$\text{MeCHClCO}_2\text{Me}$	6.3.9.A/ 40°C /88 h	73
	$\text{ToISO}_2\text{CH}_2\text{Cl}$	6.3.9.B/ 35°C /45 min	65
<i>n</i> - $\text{C}_7\text{H}_{15}\text{CHO}$	$\text{CH}_2\text{ClCO}_2\text{Et}$	6.3.9.A/ 40°C /52 h	32
	$\text{MeCHClCO}_2\text{Me}$	6.3.9.A/ 40°C /88 h	48
Me_2CO	ClCH_2CN	6.3.9.C/ 20°C	60
	$\text{ToISO}_2\text{CH}_2\text{Cl}$	6.3.9.B/ 35°C /45 min	91
cyclohexanone	ClCH_2CN	6.3.9.C/ 20°C	55
	$\text{ToISO}_2\text{CH}_2\text{Br}$	6.3.9.B/ 35°C /45 min	90

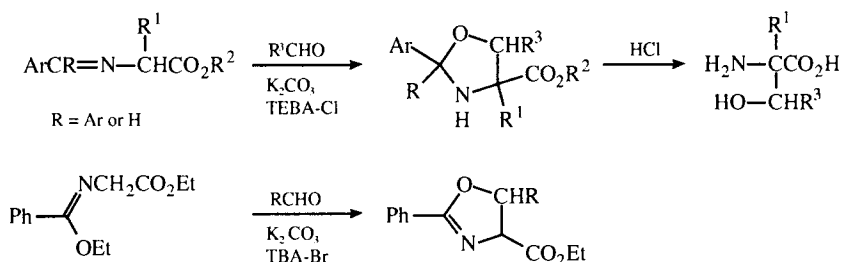
basic conditions, when catalysed by quaternary ammonium salts. Yields are generally high with aryl aldehydes (>85%), but are lower (15–40%) with aryl ketones. The oxiranes are formed in lower yield (20–30%) when trimethyloxosulphonium iodide is used; a significant by-product from the reaction is 3,5-diphenyl-1,4-thia-dioxane-*S*-oxide [32].

6.3.10 Oxiranes from sulphonium salts

Method A: Aqueous NaOH (50%, 20 ml), $\text{Me}_3\text{S}^+\text{I}^-$ (20.4 g, 0.1 mol), the aldehyde or ketone (0.1 mol), and TBA-I (0.5 g, 1.35 mmol) in CH_2Cl_2 (100 ml) are stirred at 50 °C until the aldehyde is consumed (4–48 h) and then poured onto ice (100 g). The organic phase is separated, washed well with H_2O , dried (MgSO_4), and fractionally distilled to yield the oxirane (e.g. from PhCHO, 48 h, 92%; $\text{PhCH}=\text{CHCHO}$, 4 h, 85%; PhCOMe, 72 h, 36%; PhCOPh, 72 h, 18%).

Method B (polymer-supported): The aldehyde or ketone (1.4 mmol) is added to *S,S*-dimethyl polystyrylsulphonium fluorosulphonate (2 g) suspended in CH_2Cl_2 (15 ml) and the mixture is stirred with aqueous NaOH (65%, 2 ml) and TBA-I or TBA-OH (0.6 mmol) until the carbonyl compound has been consumed. The filtered solution is extracted with H_2O (3 × 25 ml) and evaporated to yield the oxirane (e.g. from PhCHO, 3 days, 97%; PhCOMe, 1 day, 94%; PhCOPh, 4 days, 96%).

The aldol-type condensation of imino acetic esters with aldehydes under solid:liquid two-phase conditions, followed by an intramolecular nucleophilic ring closure, produces cyclic systems (85–95%), which can be hydrolysed to give serine derivatives (Scheme 6.16) [34–36]. When the reaction is catalysed by cinchonium salts [37], a high degree of stereoselectivity is achieved (see Chapter 12). The analogous reaction with *N*-ethoxycarbonylmethyl carboximidates produces diastereomeric pairs of the oxazolines [38]. Precursors for chiral 1,3-diaminopropan-2-ols have been produced in high yield by the condensation of chiral α -*N,N*-dibenzyl-amino aldehydes with nitroalkanes in the presence of tetra-*n*-butylammonium fluoride [39]. *N*-Benzylimines react with aryl aldehydes to yield aldol-type derivatives, which on hydrolysis by dilute acid produce β -aminoethanols [40]. Similarly, *N*-benzylimines and related imines react with Schiff bases to produce, after hydrolytic cleavage of the protecting group, the *N,N'*-substituted 1,2-diaminoalkanes [e.g. 41, 42].



Scheme 6.16

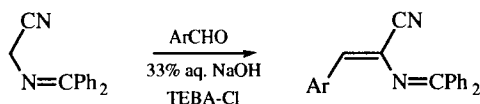
6.3.11 Tetrahydrooxazoles from imino acetic esters

The aldehyde (10 mmol) in MeCN (5 ml) is stirred with the imino ester (10 mmol), anhydrous K_2CO_3 (0.14 g) and TEBA-Cl (0.23 g, 1 mmol) in MeCN (10 ml) at room temperature until the mixture solidifies. H_2O (60 ml) is added and the solid is separated, washed well with H_2O and recrystallized (if the cyclic product does not solidify, the mixture is extracted with Et_2O (2×25 ml)). The combined extracts are washed with H_2O (25 ml), dried ($MgSO_4$) and evaporated to yield the product).

6.3.12 1-Amino-3-nitropropan-2-ols

TBA-F (1M in THF, 0.45 ml) in THF (10 ml) is added dropwise to the nitroalkane (1.2 mmol) in THF (2 ml) at $0^\circ C$. The α -*N,N*-dibenzylaminoaldehyde (0.5 mmol) in THF (4 ml) is added over 5 min and the mixture is stirred for 15 min. On completion of the reaction, the mixture is poured into aqueous $NaHCO_3$ (sat. soln., 50 ml) and extracted with Et_2O (3×50 ml). The dried ($MgSO_4$) extracts are evaporated to yield the adduct.

In contrast with the reactions of the imino esters, the aldol condensation of imino nitriles and aromatic aldehydes in dichloromethane produces azabutadienes (Scheme 6.17), with the *Z*-isomers predominating often to the exclusion of the *E*-isomers [43, 44]. Yields generally tend to be at least 10% lower when the reaction is conducted in acetonitrile.



Scheme 6.17

6.3.13 2-Azabuta-1,3-dienes

Aqueous NaOH (33%, 3 ml) is stirred with the iminonitrile (10 mmol), aryl aldehyde (11 mmol), and TEBA-Cl (0.12 g, 0.5 mmol) in CH_2Cl_2 (5 ml) for 1 h at room temperature. H_2O (100 ml) is added and the mixture is extracted with CH_2Cl_2 (3×25 ml). The dried (Na_2SO_4) extracts are evaporated and the residue is triturated with EtOH (20 ml). Evaporation of the ethanolic solution yields the 3-cyano-2-azabuta-1,3-diene (55–70%).

The condensation of aldehydes and ketones with aminoacetonitriles, although it requires more vigorous solid:liquid catalytic conditions to produce the cyano-enamines, is preferable in many respects to the traditional Wittig–Horner or Peterson procedures [45]. Hydroxyalkylphosphonates are obtained from the catalysed aldol condensation of nitromethane with acylphosphonates [46].

6.3.14 Cyanoenamines (Table 6.13)

The aminoacetonitrile (6.8 mmol) and TBA-Br (87 mg, 0.27 mmol) in PhH (2 ml) are added with stirring to powdered KOH (2.6 g, 39.5 mmol) and K_2CO_3 (1.0 g, 7 mmol) in

TABLE 6.13

Selected examples of cyanoenamines from *N*-methyl-*N*-phenylaminoacetonitriles with aldehydes and ketones

R ¹ COR ²		% yield of enamine	R ¹ COR ²		% yield of enamine
R ¹	R ²		R ¹	R ²	
Ph	H	78 ^a	Me	Me	70 ^{c,d}
<i>i</i> -Pr	H	44 ^b	Me	Et	62 ^{c,d}
	-(CH ₂) ₅ -	71 ^c			

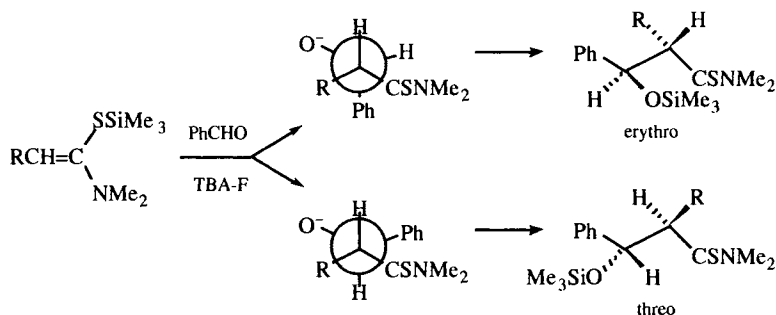
^a Reaction time 15 min. ^b Reaction time 20 min. ^c Reaction time 30 min. ^d Ketone (5 ml) used as solvent in place of PhH.

PhH (6 ml) at 50°C, followed by addition of the carbonyl compound (6.8 mmol). * The mixture is heated with stirring at 50–55°C for 15–30 min and then cooled, filtered and evaporated. Chromatography of the crude product yields the enamine (*The benzene is omitted if the ketone is used as the solvent).

6.3.15 α -Hydroxy- β -nitroalkylphosphonates

K₂CO₃ (0.5 g) and TBA-Br (0.5 g, 1.55 mmol) are added to the acylphosphonate (30 mmol) in MeNO₂ (22.5 g, 0.37 mol) and the mixture is stirred at room temperature until TLC analysis indicates the complete consumption of the phosphonate. CH₂Cl₂ (50 ml) is added and the organic solution is washed with H₂O (2 × 10 ml), aqueous NaHSO₃ (sat. soln., 2 × 20 ml) and H₂O (10 ml), dried (Na₂SO₄), and evaporated to yield the condensation product (65–80%).

The aldol condensation of benzaldehyde with the thioacetamide carbanion (RCHCSNR'₂-), derived from the desilylation of the silyl-thioether with tetra-*n*-butylammonium fluoride, is stereoselective at -80°C producing the erythro isomer of the β -hydroxy thioamide preferentially (Scheme 6.18, R = Me, erythro:threo 95 : 5) via a conformationally mobile intermediate. However, when R is bulky, a greater amount of the threo isomer is formed. Predictably, as the reaction temperature is raised, so the stereoselectivity decreases. This procedure contrasts with the corresponding condensation catalysed by titanium salts, where the complexed intermediate produces the threo isomer [47, 48].



Scheme 6.18

Fluoride ion promoted cleavage of propynylsilanes and subsequent reaction of the carbanion with carbonyl compounds produces allenic compounds. The reaction with formaldehyde and pivaldehyde fails, but both the allenic and acetylenic products are obtained from the reaction with acrolein and benzaldehyde [49]. Allylsilanes react with carbonyl compounds to produce but-3-en-1-ols [50].

6.3.16 4-Hydroxybuta-1,2-dienes

TBA-F (1M in THF, 0.2 ml) is added to $\text{Me}_3\text{SiCH}_2\text{C}\equiv\text{CH}$ (0.56 g, 4 mmol) and the carbonyl compound (4 mmol) in THF (10 ml) at -5° to 0°C . On completion of the reaction (Table 6.14), the mixture is washed sequentially with methanolic HCl and aqueous Na_2CO_3 . Et_2O is added and the filtered solution is dried (K_2CO_3) and fractionally distilled to yield the allenic alcohol.

TABLE 6.14
Selected examples of 4-hydroxybuta-1,2-dienes and 4-hydroxybut-1-ynes

R ¹ COR ²		Reaction conditions	% yield	
R ¹	R ²		$\text{CH}_2=\text{C}=\text{CHCR}^1\text{R}^2\text{OH}$	$\text{CH}\equiv\text{CCH}_2\text{CR}^1\text{R}^2\text{OH}$
Me	H	6.3.16 / $-5^\circ\text{C}/3\text{ h}$	65	0
Et	H	6.3.16 / $0^\circ\text{C}/1\text{ h}$	60	0
<i>n</i> -Pr	H	6.3.16 / $0^\circ\text{C}/1\text{ h}$	67	0
<i>n</i> -Bu	H	6.3.16 / $0^\circ\text{C}/1\text{ h}$	80	0
<i>i</i> -Pr	H	6.3.16 / $60^\circ\text{C}/16\text{ h}$	53	0
$\text{CH}_2=\text{CH}$	H	6.3.16 / $0^\circ\text{C}/4\text{ h}$	20	5
Ph	H	6.3.16 / $50^\circ\text{C}/16\text{ h}$	32	13
Et	Et	6.3.16 / $60^\circ\text{C}/16\text{ h}$	15	0
$-(\text{CH}_2)_5-$		6.3.16 / $20^\circ\text{C}/20\text{ h}$	10	0

6.3.17 But-3-en-1-ols

The carbonyl compound (2 mmol) and the allylsilane (2 mmol) in THF (5 ml) is added at room temperature to TBA-F (26 mg, 0.1 mmol) and 4Å molecular sieves (50 mg) in THF (5 ml). The mixture is stirred for 8 h to yield the but-3-enyl silyl ether. The solvent is removed and the residue is refluxed for 4 h in methanolic HCl. Evaporation of the methanol yields the but-3-en-1-ol (60–90%).

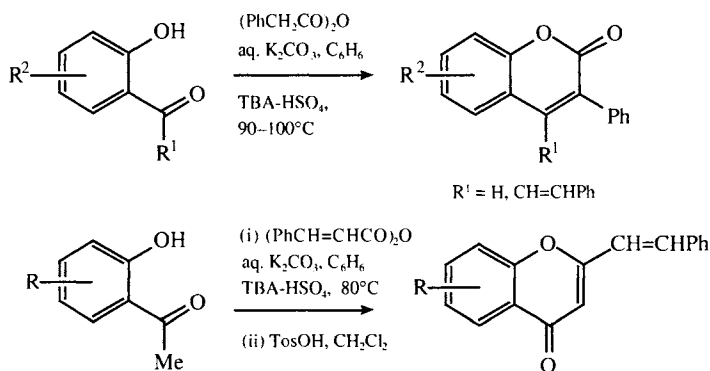
Triethylammonium formate–formic acid complex, $(\text{HCO}_2\text{NHEt}_3)_2(\text{HCO}_2\text{H})_3$, is used in a one-pot reductive aldol condensation of Meldrum's acid with aldehydes to produce the alkylated derivative [51]. Although feasible, the process has not been adapted for use with a quaternary ammonium formate salt.

6.3.18 Reductive aldol condensation of Meldrum's acid with aldehydes

Meldrum's acid (72 g, 0.5 mol) is added with stirring at room temperature to the aldehyde (0.5 mol) suspended in the triethylammonium formate complex (500 ml), or with the

triethylammonium formate complex (150 ml) in DMF (100 ml). The initial aldol adduct precipitates from solution and the mixture is stirred for a further 2–4 days at room temperature and then poured into ice–water (11) and acidified to pH 2 with HCl (6 M). The monoalkylated malonic acid (70–78%) precipitates.

One-pot conversions of 2-hydroxy(acylbenzenes) with anhydrides or acid chlorides to produce coumarins [52–54] and flavones [54–58] under mild liquid:liquid or solid:liquid two-phase conditions via a Baker–Venkataraman type reaction (Scheme 6.19) are catalysed by quaternary ammonium salts. 3-Substituted coumarins are produced from salicylaldehyde and malonodinitrile, or substituted acetonitriles, in high yield (>85%) in a one-pot catalysed sequential aldol-type reaction and cyclization in the absence of an added organic solvent [59]. When 2'-hydroxychalcones are reduced under catalytic two-phase conditions with sodium borohydride, 2,4-*cis*-flavan-4-ols are produced [60] (see Section 11.3).



Scheme 6.19

6.3.19 2-Substituted chromones

Method A: The 2-hydroxyacetophenone (3 mmol) and acyl chloride (3.6 mmol) in PhH (20 ml) are stirred at 80°C with aqueous K_2CO_3 (10%, 20 ml) and TBA- HSO_4 (0.5 g, 1.5 mmol) for 2–3 h until the ester is completely formed. The PhH phase is separated, washed with H_2O (3×20 ml) and dried by azeotropic distillation. Ring closure is effected by the addition of TosOH (1.55 g, 9 mmol) in PhH (20 ml) and azeotropic distillation. The organic solution is washed with aqueous NaHCO_3 (10%, 50 ml) and evaporated to yield the chromone.

Method B: The acyl chloride (12 mmol) in CH_2Cl_2 (10 ml) is added dropwise over 15 min to the 2-hydroxyacetophenone (10 mmol), TBA- HSO_4 (0.1 g, 0.3 mmol) and aqueous K_2CO_3 (20%, 30 ml) at room temperature. The mixture is stirred for *ca.* 7 h and the organic phase is then separated, washed well with H_2O and brine, dried (MgSO_4), and evaporated to yield the chromone (70–95%).

6.3.20 Base-catalysed synthesis of coumarins under liquid:liquid phase-transfer catalysis

The 2-acylphenol (2.2 mmol), $(\text{PhCH}_2\text{CO})_2\text{O}$ (0.75 g, 2.5 mmol) and TBA- HSO_4 (0.34 g, 1 mmol) in PhH (20 ml) are stirred with aqueous K_2CO_3 (sat. soln., 20 ml) at 90–100°C until the reaction is complete, as shown by TLC analysis. The organic phase is separated, washed well with H_2O , dried (Na_2SO_4), and evaporated to yield the coumarin (65–85%).

6.3.21 Typical syntheses of flavones under liquid:liquid phase-transfer catalysis

Method A: Following procedure 6.3.19, the crude aldol condensation product from 2-hydroxyacetophenone (5 mmol) and $(\text{PhCH}=\text{CHCO})_2\text{O}$ (1.63 g, 5 mmol) is taken up in CH_2Cl_2 (10 ml) and heated under reflux with TosOH (1 g) for 30 min. Water is added and the precipitated flavone (~75%) is collected.

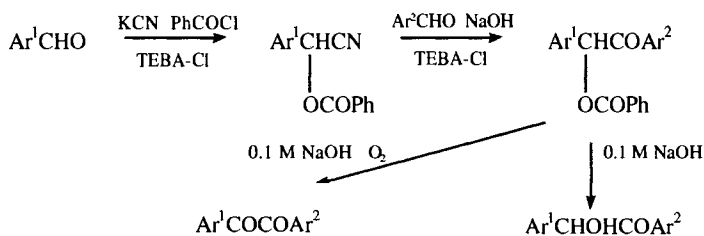
Method B: The acid chloride (3.6 mmol), the 2-hydroxyacetophenone (3 mmol), and TBA- HSO_4 (0.5 g, 1.5 mmol) in PhH (20 ml) are refluxed with aqueous K_2CO_3 or KOH (10%, 20 ml) for 2–3 h until the ester is completely formed. The organic phase is separated, washed well with H_2O , dried (MgSO_4), and evaporated. The residue is taken up in PhH (50 ml) containing TosOH (1.5 g) and cyclized by azeotropic distillation to yield the flavone (>90%). Alternatively, the residue is stirred for 4 h in concentrated H_2SO_4 (4 ml) at 0°C and then poured onto ice to yield the flavone.

Method C: The acid chloride (12 mmol) in CH_2Cl_2 (10 ml) is added dropwise over ca. 15 min with stirring to the 2-acylphenol (10 mmol) and TBA- HSO_4 (0.1 g, 0.3 mmol) in CH_2Cl_2 (30 ml) and aqueous K_2CO_3 (20%, 30 ml). The mixture is stirred for ca. 8 h at room temperature and the flavone is isolated using the procedure described in 6.3.19.

The rate of the base-catalysed condensation of carbonyl compounds with alkyl groups activated by π -deficient aromatic systems is enhanced by the addition of quaternary ammonium salts. For example, 2-methylbenzoxazole, 2-methylbenzothiazole and 4-nitrotoluene react with a range of substituted benzaldehydes to produce the corresponding 2-styryl derivatives (62–80%) at room temperature over 1–2 hours [61, 62]. The intermediate alcohol can also be isolated after a short reaction time.

Tetra-*n*-butylammonium cyanide is a better catalyst for benzoin condensation reactions than is sodium cyanide, and >70% yields are obtained under mild conditions [63, 64]; tetra-ethylammonium cyanide is less effective. Polymer-supported ammonium catalysts have also been used to promote the benzoin reaction and, although yields are only moderate (40–60%), the convenience of removal of the catalyst is an advantage. Use of chiral ammonium groups produces an enantiomeric excess of chiral products from the condensation of benzaldehyde, but furfural tends to produce a racemate [65].

Regio-control of the formation of benzoic esters of mixed benzoin derivatives results from the initial formation of the cyanhydrin benzoate (see Chapter 3). Subsequent base-catalysed hydrolysis of the esters produces the mixed benzoin (Scheme 6.20) [66].



Scheme 6.20

6.3.22 Mixed benzoin benzoates

KCN (2 g, 30 mmol) in H₂O (6 ml) is added dropwise to the aryl aldehyde (20 mmol) and PhCOCl (3.6 g) in CH₂Cl₂ (2 ml) at 0°C. TEBA-Cl (150 mg, 0.65 mmol) is added and the mixture is stirred overnight at room temperature. The acylated cyanhydrin is worked up as described in 3.3.9.B.

Aqueous NaOH (50%, 0.2 ml), TEBA-Cl (15 mg, 0.06 mmol), and the cyanhydrin benzoate (1 mmol) in PhH (4 ml), are stirred at room temperature under argon for 10 min. The aryl aldehyde (1 mmol) in PhH (4 ml) is then added at 0°C and the mixture is stirred at room temperature for *ca.* 5 h (monitored by TLC). On completion of the reaction, the organic solution is separated and washed well with H₂O, dried (MgSO₄), and evaporated to yield the benzoin benzoate (Table 6.15).

Carbanions, generated by the reaction of benzylsilanes with tetra-*n*-butylammonium fluoride react with non-enolizable aldehydes to produce the alcohol [67]. When a stoichiometric amount of the ammonium fluoride is used, the methylene corresponding to the benzylsilane is frequently a by-product and arises from formation of the hydrogen difluoride salt during the reaction. When only catalytic amounts of the ammonium fluoride initiate the reaction, the formation of the methylene is suppressed. In a similar type of reaction (although the mechanism is not known) between aldehydes and ketones, allyl bromide, and tin in the presence of trimethylsilyl chloride the yield of the but-1-en-4-ol is raised significantly by the addition of tetra-*n*-butylammonium bromide, particularly in the reactions with

TABLE 6.15
Selected examples of mixed benzoin benzoates

Ar ¹ CHO	Ar ² CHO	% yield of Ar ¹ CH(OCOPh)COAr ²
4-BrC ₆ H ₄ CHO	4-BrC ₆ H ₄ CHO	68
4-CNC ₆ H ₄ CHO	4-CNC ₆ H ₄ CHO	77
4-O ₂ NC ₆ H ₄ CHO	4-O ₂ NC ₆ H ₄ CHO	80
4-MeC ₆ H ₄ CHO	PhCHO	40
4-O ₂ NC ₆ H ₄ CHO	PhCHO	85
PhCHO	4-MeC ₆ H ₄ CHO	72
PhCHO	4-BrC ₆ H ₄ CHO	63

ketones [68]. A similar reaction of ethyl trimethylsilylacetate with aldehydes and ketones produces β -silyloxypropanoates [69] and aryl aldehydes react with 1,1-difluoro-3-trimethylsilylprop-1-ene, promoted by the addition of a stoichiometric amount of tetra-*n*-butylammonium fluoride to produce 1-aryl-2-hydroxy-3,3-difluorobut-3-enes (75–85%), which probably arise via an elimination–addition mechanism [70].

Under basic liquid:liquid two-phase conditions the reaction of aryl aldehydes with benzyldibutyltelluronium bromide produces oxiranes [71] although, in some instances, alkenes are formed.

6.3.23 1-Arylalkan-2-ols

TBA-F (1M in THF, 0.25 ml, 0.25 mmol) in THF (5 ml) is added dropwise with stirring to the trimethylsilylmethylarene (5 mmol) and the aldehyde (6 mmol) in THF (10 ml) under N_2 . The mixture is stirred at room temperature for 15 min. Concentrated HCl (5 ml) is then added and the mixture is extracted with Et_2O (4×25 ml). The combined extracts are dried ($MgSO_4$) and evaporated to yield the crude alkanol (e.g. from $PhCH_2SiMe_3$: 60% with $PhCHO$; 74%, H_2CO ; 78%, CCl_3CHO ; 69%, $MeCH=CHCHO$).

6.3.24 β -Trimethylsilyloxypropanoates

$Me_3SiCH_2CO_2Et$ (4.07 g, 25.4 mmol) and the aldehyde or ketone (25 mmol) in THF (10 ml) are added over 10 min to TBA-F (42 mg, 0.16 mmol) in THF (2 ml) at $-78^\circ C$. The mixture is stirred at $-78^\circ C$ for 5 min and then at room temperature for *ca.* 3 h. *n*- C_6H_{12} (25 ml) is added and the solution is filtered and fractionally distilled to yield the adduct (e.g. from $PhCHO$, 76%; $PhCH=CHCHO$, 81%; $PhCOPh$, 88%; *trans n*- $PrCH=CHCHO$, 82%; $MeCH=CHCHO$, 69%).

6.3.25 Oxirane formation from telluronium salts

$Bu_2TeCH_2Ph^+Br^-$ (0.45 g, 1.1 mmol) and TBA-Br (0.1 g, 0.3 mmol) in CH_2Cl_2 (5 ml) are added to aqueous NaOH (50%, 1 ml). The aryl aldehyde (1 mmol) in CH_2Cl_2 (1 ml) is added dropwise and the mixture is stirred until complete as shown by HPLC analysis. The aqueous phase is separated and extracted with CH_2Cl_2 (2×20 ml). The combined organic solutions are dried ($MgSO_4$) and evaporated to yield the oxirane (e.g. from $PhCHO$, 4 h, 75%; 4- FC_6H_4CHO , 2 h, 89%; 4- ClC_6H_4CHO , 2 h, 87%; 4- $O_2NC_6H_4CHO$, 2 h, 84%).

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6.4 MICHAEL REACTIONS AND OTHER RELATED REACTIONS

Examples of the Michael-type addition of carbanions, derived from activated methylene compounds, with electron-deficient alkenes under phase-transfer catalytic conditions have been reported [e.g. 1–17] (Table 6.16). Although the basic conditions are normally provided by sodium hydroxide or potassium carbonate, fluoride and cyanide salts have also been used [e.g. 1, 12–14]. Solid:liquid two-phase systems, with or without added organic solvent [e.g. 15–18] and polymer-supported catalysts [11] have been employed, as well as normal liquid:liquid conditions. The micellar ammonium catalysts have also been used, e.g. for the condensation of β -dicarbonyl compounds with but-3-en-2-one [19], and they are reported to be superior to tetra-*n*-butylammonium bromide at low base concentrations.

Reactions involving ketones are generally controlled by the thermodynamic stability of the enolate anion. However, 2-phenylcyclohexanone reacts with bulky Michael acceptors to form the 2,6-regioisomer preferentially [17], indicating that the reaction is mainly kinetically controlled with the approach of the Michael acceptor to the substituted 2-position being sterically hindered.

The reactivity of phenylacetic esters with electron-deficient alkenes is generally fairly poor, even under phase-transfer catalytic conditions. The reaction with cinnamic esters is often accompanied by hydrolysis and the yield of the adduct with chalcone is generally <60% [10]. The activity of the methylene group towards alkylation has been enhanced by the initial complexation of the phenyl ring with chromium tricarbonyl (see Section 6.2), but this procedure has not been applied to the Michael reaction.

Michael adducts (Table 6.16) are obtained from the reaction of malonic esters and

TABLE 6.16

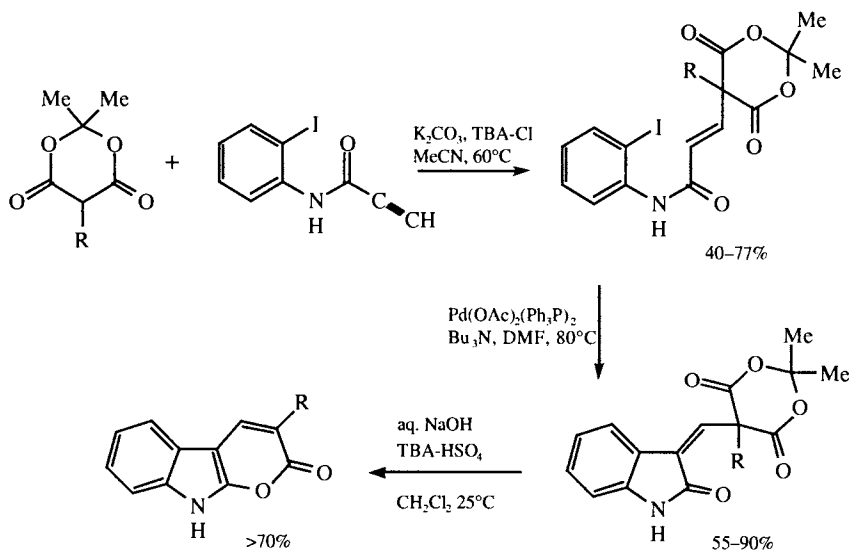
Selected examples of the Michael-type addition of activated methylene compounds with electron-deficient alkenes

Methylene compound	Alkene	Reaction conditions	% yield
(EtS) ₂ CHCO ₂ Et	CH ₂ =CHCOMe	6.4.1.C/1.5 h/80 °C	89
	CH ₂ =CHCO ₂ Me	6.4.1.C/1.5 h/80 °C	91
	CH ₂ =CHCN	6.4.1.C/1.5 h/80 °C	86
	CH ₂ =CHCHO	6.4.1.C/1.5 h/20 °C	30
	Cyclohex-2-enone	6.4.1.C/1.5 h/80 °C	35
(EtS) ₂ CHCN	CH ₂ =CHCOMe	6.4.1.C/20 min/20 °C	94
	CH ₂ =CHCO ₂ Me	6.4.1.C/1.2 h/20 °C	92
	CH ₂ =CHCN	6.4.1.C/1.5 min/20 °C	94
	CH ₂ =CHCHO	6.4.1.C/1 h/ 0 °C	7 ^a
	Cyclohex-2-enone	6.4.1.C/1 h/20 °C	88
PhCH ₂ CN	ArCH=CHMe ^b	6.4.1.A/1–3 h/rt	84–92
PhCHMeCN	ArCH=CHMe ^b	6.4.1.A/4–8 h/rt	67–75
PhCH ₂ CO ₂ <i>t</i> -Bu	PhCH=CHCN	6.4.1.A/2 h/rt	75
CH ₂ (COMe) ₂	PhCH=CHCOPh	6.4.1.D/16 h/20 °C	77
MeCOCH ₂ CO ₂ Me	PhCH=CHCOPh	6.4.1.D/16 h/20 °C	77
	CH ₂ =CHCHO	6.4.1.C ^d /15 min/45 °C	48
	MeCH=CHCHO	6.4.1.C ^d /2 h/45 °C	55 ^e
CH ₂ (CO ₂ Et) ₂	CH ₂ =CHCHO	6.4.1.C ^d /3 h/45 °C	50
	MeCH=CHCHO	6.4.1.C ^d /4 h/45 °C	60
	PhCH=CHCHO	6.4.1.C ^d /2 h/45 °C	65
EtNO ₂	CH ₂ =CHCOMe	6.4.1.E/4 h/rt	76
	CH ₂ =CHCO ₂ Me	6.4.1.E/6 h/rt	76
	Cyclohex-2-enone	6.4.1.E/20 h/rt	93
Me ₂ CHNO ₂	CH ₂ =CHCOMe	6.4.1.E/20 h/rt	75
	CH ₂ =CHCO ₂ Me	6.4.1.E/4 h/rt	80 ^f
PhCH ₂ NO ₂	CH ₂ =CHCO ₂ Me	6.4.1.E/6 h/rt	78
PhSO ₂ CH ₂ CH=CMe ₂	CH ₂ =CHCN	6.4.1.B/1.5 h/35 °C	72
	CH ₂ =CHSO ₂ Ph	6.4.1.B/1.5 h/35 °C	73
	CH ₂ =CHCO ₂ <i>t</i> -Bu	6.4.1.B/1.5 h/35 °C	76 ^g
PhSO ₂ CH ₂ CH=CH ₂	CH ₂ =CHCN	6.4.1.B/1.5 h/35 °C	61 ^h
PhCH=NCH ₂ CO ₂ Et	CH ₂ =CHCO ₂ Me	6.4.1.C/2 h/rt	93
	CH ₂ =CHCN	6.4.1.C/2 h/rt	92
PhCH=NCHMeCO ₂ Me	CH ₂ =CHCO ₂ Me	6.4.1.C/2 h/rt	92
	PhCH=CHCO ₂ Me	6.4.1.C/2 h/rt	94
	CH ₂ =CHCN	6.4.1.C/2 h/rt	90

^a + 12% of aldol product from initial Michael addition. ^b Ar = 2-methoxy-4-substituted benzene. ^c In MeCN. ^d PhH.^e 5-phenylcyclohex-2-enone. ^f The addition can be conducted under liquid:liquid conditions with TBA-CN. ^g Isolated as the acid. ^h Double Michael reaction giving TolSO₂C[(CH₂)₂CN]₂CH=CH₂.

β-keto esters with α,β-unsaturated aldehydes liquid:liquid two-phase conditions [20] but, in contrast, under analogous conditions α-cyanoacetic esters produce aldol adducts with α,β-unsaturated aldehydes [20]. Ethyl acetoacetate undergoes a catalysed Michael reaction addition with *trans* but-2-en-1,4-diones; the products are generally insufficiently stable for isolation, but can be converted into furans [21].

Meldrum's acid reacts with electron-deficient alkenes providing a convenient route to the C-alkylated Meldrum's acid derivatives [22, 23] (see also 6.2.24). Controlled stepwise dialkylation is possible by this procedure, thereby permitting the introduction of different groups. The analogous reaction of Meldrum's acid with alkynes produces the C-alkenyl derivatives which, in the case of the 2-oxoprop-1-enyl derivatives, undergo ring-opening and conversion into pyran-2-ones [24]. The corresponding reaction between Meldrum's acid and propynoyl anilides follows an analogous pathway. With 2-iodoanilides, a subsequent Heck reaction, followed by cleavage of the substituted Meldrum's acid and ring-closure leads to pyranoindoles (Scheme 6.21) [25].



Scheme 6.21

6.4.1 Michael-type addition of activated methylene compounds to electron-deficient alkenes

Method A: Aqueous NaOH (ca. 18 M, 3.5 ml) is added to the methylene compound (2 mmol), the alkene (1 mmol), and TBA-Br (0.3 mmol) in degassed PhCl (10 ml). The mixture is stirred under N_2 at room temperature until GLC analysis shows the reaction to be complete and then diluted with H_2O (50 ml). The aqueous mixture is extracted with CH_2Cl_2 (3×25 ml) and the extracts are washed well with H_2O , dried ($MgSO_4$), and evaporated to yield the adduct.

Method B: The methylene compound (15 mmol) and the alkene (30 mmol) and TBA-Br (0.24 g, 0.75 mmol) in HMPT (1.8 ml) are stirred with aqueous NaOH (50%, 15 ml) for 15 min at 30 – $35^\circ C$. The mixture is then diluted with H_2O (25 ml) and extracted with $CHCl_3$ (2×25 ml). The extracts are washed well with HCl (2M), H_2O , and brine, dried ($MgSO_4$), and evaporated to yield the adduct.

Method C (solid:liquid process): Anhydrous K_2CO_3 (2.8 g), TEBA-Cl (0.23 g, 1 mmol), the methylene compound (10 mmol) and the alkene (10 mmol) in MeCN or CH_2Cl_2 (30 ml) are stirred at room temperature for *ca.* 2 h and the mixture is then filtered and evaporated. Et_2O (25 ml) is added to the residue and the filtered ethereal extract is washed with H_2O (15 ml), dried ($MgSO_4$), and evaporated to yield the Michael adduct.

Method D (solid:liquid process without organic solvent): The alkene (10 mmol) and the methylene compound (10 mmol) are shaken with powdered KOH (0.34 g, 6 mmol) and TEBA-Cl (0.14 g, 0.6 mmol) at 20°C for 16 h (or 2 h at 60°C). The adduct is isolated using the procedure described in 6.4.1.C.

Method E (polymer supported catalyst): The alkene (50 mmol) is added to the activated methylene compound (50 mmol) at 0°C and the mixture is stirred for 10 min. Amberlyst A-27 (8 g) is added and the mixture is stirred for a further 15 min and then allowed to stand at room temperature for 4–25 h. The polymer is removed and washed with Et_2O (4 × 40 ml). The combined organic solutions are evaporated and the residue subjected to flash chromatography to yield the Michael adduct (75–95%).

6.4.2 Furans

The *trans*-but-2-en-1,4-dione (8.4 mmol) and the methylene compound (8.4 mmol) are stirred with Na_2CO_3 (98 mg) and TEBA-Cl (20 mg) in PhH (10 ml) at 75–80°C until the reaction is complete, as shown by TLC analysis (*ca.* 24 h with β -keto esters and *ca.* 48 h with cyclohexa-1,3-dione). Et_2O (50 ml) is added and the organic phase is washed well with brine. Evaporation of the ethereal solution gives the unstable adduct but, if the ethereal solution is saturated with HCl gas, the adduct is converted into the furan (overall yields >45%).

6.4.3 Reaction of Meldrum's acid with electron-deficient alkenes

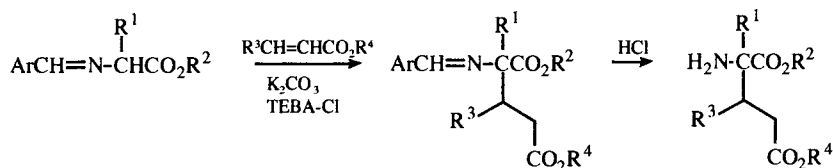
K_2CO_3 (1.38 g) and TEBA-Cl (2.28 g, 10 mmol) are stirred with Meldrum's acid (1.4 g, 10 mmol) in MeCN (10 ml) at room temperature for 15 min. The alkene (15 mmol) in MeCN (5 ml) is then added and the mixture stirred at 50–60°C for *ca.* 8–10 h until the reaction is complete, as shown by TLC analysis. The mixture is cooled to room temperature and H_2O (50 ml) is added. The aqueous solution is washed with Et_2O (2 × 20 ml) and the solution is adjusted to pH 2 with HCl (6M) causing the precipitation of the adduct [from $CH_2=CHCOMe$, 90%; $CH_2=CHCO_2Et$, 94%; $CH_2=CHCN$, 93%; $MeO_2CC=CHCO_2Me$, 70%].

6.4.4 2H-Pyran-2-ones

The Meldrum's acid derivative (0.87 mmol), and the ethynyl ketone (1.3 mmol) are stirred with K_2CO_3 (0.12 g) and TBA-Cl (0.26 g, 0.87 mmol) in MeCN (2 ml) at 60°C for 1–2 h. H_2O (20 ml) and EtOAc (20 ml) are then added and the organic phase is separated, washed well with H_2O , dried (Na_2SO_4), and evaporated to yield the pyranone (40–80%).

Michael addition of methylene imines with alkenes under solid:liquid two-phase conditions provides a route to substituted α -amino acids [26, 27] (Scheme 6.22). When ethyl glycine is *N*-protected with (*S*)-menthone, *C*-alkylation under solid:liquid

conditions provides a route to chiral α -substituted amino acids with optimum enantiomeric excesses of 46–47% [28]. Analogous reactions between α,β -unsaturated ketones and arylmethylimines have been reported [e.g. 29].

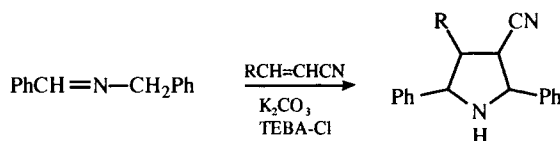


Scheme 6.22

6.4.5 Chiral α -amino acids

The electron-deficient alkene (5.2 mmol) in MeCN (5 ml) is added to an intimate mixture of powdered K_2CO_3 (1 g) and NaOH (0.2 g), the (*S*)-menthone-protected ethyl glycine (1.27 g, 5 mmol), and TBA-Br (0.16 g, 0.5 mmol) in MeCN (20 ml). The mixture is stirred for 1 h at 0°C and then filtered. The solid is washed with MeCN (10 ml) and the combined organic solutions are evaporated and the residue is taken up in Et_2O . The ethereal solution is washed well with H_2O , dried (MgSO_4), and evaporated to produce the alkylated imine, which can be converted into the amino acid upon hydrolysis with aqueous acid.

N-Benzylimines have also been reported to react with acrylonitriles under solid:liquid conditions in which the initial anionic intermediate undergoes an intramolecular nucleophilic ring closure to produce a diastereoisomeric mixture of the pyrrolidine (Scheme 6.23) [30–32]. Similar cyclized products have been reported for the reaction of benzylidene-protected α -amino esters and vinyl ketones [33, 34].



Scheme 6.23

Conversely, activated methylene compounds undergo an addition reaction across the $\text{C}=\text{N}$ bond of imines. For example, benzylic ketones react with benzylidene anilines to form β -aminoketones [35], whereas the analogous reaction of diphenylmethylene-protected α -amino esters, and nitriles, produces a diastereoisomeric mixture of the *N*-protected α,β -diamino esters, and nitriles [36, 37].

6.4.6 Michael-type addition of activated methylene compounds to imines (Table 6.17)

Aqueous NaOH (50%, 3 ml) is stirred at 0°C with the methylene compound (5 mmol), the benzylideneaniline (0.9 g, 5 mmol), and TEBA-Cl or Aliquat (0.5 mmol) in MeCN

TABLE 6.17

Selected examples of the Michael-type addition of activated methylene compounds with imines

Methylene compound	Imine	Reaction conditions	% yield
PhCH ₂ COMe	PhCH=NPh	24 h/rt	79
	4-ClC ₆ H ₄ CH=NPh	24 h/rt	51
PhCH ₂ COPh	PhCH=NPh	24 h/rt	79
	4-ClC ₆ H ₄ PhCH=NPh	24 h/rt	73
PhCH ₂ CO ₂ <i>t</i> -Bu	PhCH=NPh	2 h/rt	75
Ph ₂ C=NCH ₂ CO ₂ Et	PhCH=NPh	10 min/rt	56

(5 ml) for *ca.* 10 min. The precipitated product is collected, washed well with water and is recrystallized from MeOH to yield the α,β -diamino derivative.

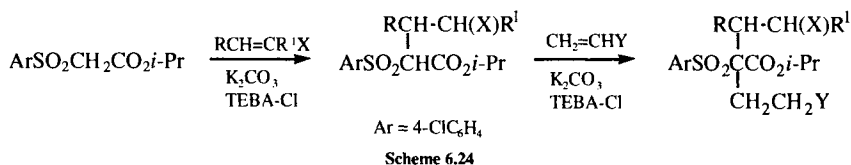
6.4.7 Pyrrolidines

Method A: The *N*-benzylimine (10 mmol), the acrylonitrile (10 mmol), and TEBA-Cl (10.2 g, 0.5 mmol) in DMSO or CH₂Cl₂* (5 ml) are stirred with aqueous NaOH (50%, 3 ml) for 30 min and then allowed to stand overnight. H₂O (100 ml) is added and the precipitated pyrrolidine is collected [* yields are higher (60–80%) in DMSO].

Method B: The protected α -amino ester (10 mmol) and α,β -unsaturated ketone (10 mmol) are stirred with K₂CO₃ (0.28 g) and TEBA-Cl (0.23 g, 1 mmol) at room temperature until the mixture solidifies. The mixture is allowed to stand for 10 h, and H₂O (100 ml) is then added. The precipitated pyrrolidine is collected, washed with H₂O, and recrystallized from MeOH.

Phenylacetonitriles can be induced to undergo Michael reactions with unactivated alkenes. For example, propenylarenes, formed *in situ* from allylarenes, react with phenylacetonitriles to form 3-aryl-1-cyano-2-methyl-1-phenylpropanes (70–98%) [3] by a procedure analogous to 6.4.1.B. Similarly, the nitriles react with alkynes giving allyl cyanides (80–95%) [38].

Most aryl alkyl sulphones react with electron-deficient alkenes in the expected manner [e.g. 4–8] and α -(arenesulphonyl)acetic esters undergo a catalysed one-pot ‘double Michael addition’ with Michael acceptors (Scheme 6.24) [8]. The two Michael acceptors can be either identical or different.



6.4.8 One-pot single and double Michael addition reactions (Table 6.18)

The reactive alkene (5 mmol) is added dropwise to the arenesulphonylacetic ester (4 mmol), K₂CO₃ (0.83 g) and TEBA-Cl (0.7 g, 0.3 mmol) in DMF (50 ml) at 40°C and

TABLE 6.18

Selected examples of single and double Michael addition reactions with $\text{PhSO}_2\text{CH}_2\text{CO}_2i\text{-Pr}$ (Scheme 6.24)

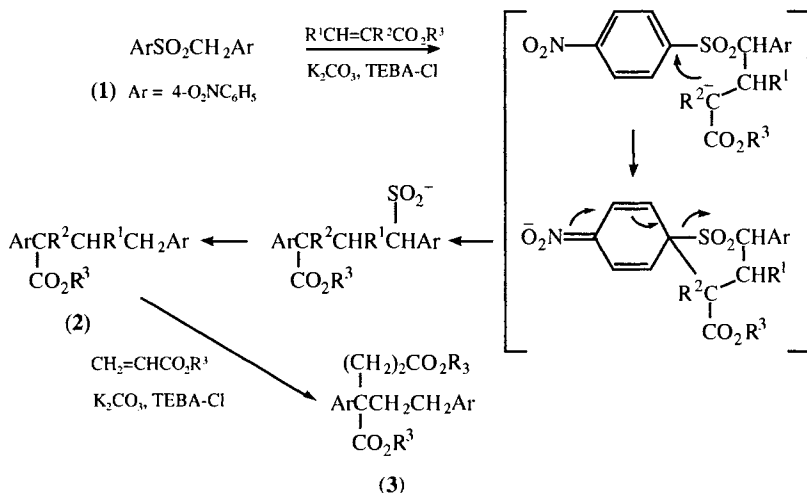
R	$\text{RCH}=\text{R}^1\text{X}$		$\text{CH}_2=\text{CHY}$ Y	Reaction time	% yield ^a
	R ¹	X			
H	Me	CO_2Me	—	2 h	89(s)
H	$\text{CH}_2\text{CO}_2\text{Et}$	CO_2Et	—	1.5 h	90(s)
Me	H	$\text{CO}_2i\text{-Pr}$	—	3 h	85(s)
CO_2Me	CO_2Me	H	—	3.5 h	74(s)
H	Me	CO_2Me	CO_2Et	2 + 2 h	80(d)
H	Me	CO_2Me	CN	2 + 2 h	55(d)
H	H	CO_2Et	CO_2Et	1 + 1 h ^b	92(d)

^a (s) single adduct; (d) double adduct. ^b at 50°C.

the mixture stirred until the reaction is complete (1.5–3.5 h), as shown by TLC analysis. The mixture is poured into H_2O (200 ml), neutralized with aqueous HCl (1M), and extracted with CH_2Cl_2 (3×15 ml). The extracts are washed with H_2O (2×10 ml), dried (Na_2SO_4), and fractionally distilled to yield the mono-Michael adduct.

The reaction is conducted as above but, after the first reaction is complete, the second alkene (0.5 mol) in DMF (5 ml) is added and the mixture is stirred for a further 2–3 h. The double Michael adduct is isolated as described above.

However, in an intriguing reaction promoted by the *para*-nitro groups of the arylsulphone (1) (Scheme 6.25), the initial Michael adduct derived from acrylic esters produces the diarylpropanoic esters (2), together with the diesters (3) (from methyl or ethyl acrylate) [39]. A similar addition–rearrangement reaction has been observed with 1-aryl-2-(4-nitrobenzenesulphonyl)ethanones [40]. Additionally, reaction of the sulphonylethanone with two equivalents of the acrylic ester produces a 4-hydroxy-1,4-diarylcylohexane-1,3-dicarboxylate.



Scheme 6.25

6.4.9 1,3-Diarylpropanoic esters

The benzyldisulphone **1** (2 mmol) in DMF (95 ml) is stirred with anhydrous K_2CO_3 (0.55 g) and TEBA-Cl (0.1 g, 0.44 mmol) for 15 min at room temperature. The acrylic ester (6 mmol) is added and the mixture is stirred at 75 °C. On completion of the reaction, as shown by TLC analysis, the cooled mixture is poured into H_2O (250 ml) and the pH adjusted to 6.5 with aqueous HCl (2 M). The aqueous solution is extracted with CH_2Cl_2 (3×15 ml) and the extracts are dried (Na_2SO_4) and evaporated to yield the propanoic esters **2** (R^1, R^2, R^3 , reaction time, % yield: H, H, Me, 5 h, 95%; H, Me, Me, 5 h, 92%; H, CH_2CO_2Me , Me, 6 h, 91%; H, H, Et, 4 h, 94%; H, Me, Et, 5 h, 90%; Me, H, Me, 10 h, 85%). The diesters **3** ($R^3 = Me$ 93%; $R^3 = Et$ 90%) are obtained by reaction with double the amount of the acrylic ester (12 mmol).

Nitroalkanes react with π -deficient alkenes, for example, β -nitro ketones are produced from α,β -unsaturated ketones [41], whereas allylic nitro compounds have been prepared via the Michael-type addition of nitroalkanes with electron-deficient alkynes (Table 6.19). The reaction in either dimethylsulphoxide [42] or dimethylformamide [43] is catalysed by potassium fluoride in the presence of benzyltriethylammonium chloride; the reaction with dimethyl acetylenedicarboxylate is only successful in dimethylsulphoxide [42]. Primary nitroalkanes produce 'double' Michael adducts [42, 44]. *N*-Protected α -aminoacetonitriles react with alkynes under catalysed solid:liquid conditions to produce the Michael adducts [45] which, upon treatment with aqueous copper(II) sulphate, are converted into α,β -unsaturated ketones.

6.4.10 β -Nitro ketones

The α,β -unsaturated ketone (10 mmol) is stirred with the nitroalkane (40 mmol), K_2CO_3 (0.7 g) and Aliquat (40 mg, 0.1 mmol) and the mixture is subjected to sonication at room temperature until the reaction is complete, as shown by GLC. The mixture is acidified with HCl (1M) and extracted with Et_2O (3×20 ml). The dried ($MgSO_4$) extracts are evaporated to yield the nitro ketone (>70%).

TABLE 6.19
Selected examples of the Michael-type addition of secondary
nitroalkanes with electron-deficient alkynes

Nitromethane	Alkene	% yield
Me_2CHNO_2	$CH \equiv CCOMe$	80
	$CH \equiv CCO_2Me$	90
	$MeO_2CC \equiv CCO_2Me$	62
cyclo- $C_6H_{11}NO_2$	$CH \equiv CCOMe$	80
	$CH \equiv CCO_2Me$	90
	$MeO_2CC \equiv CCO_2Me$	75

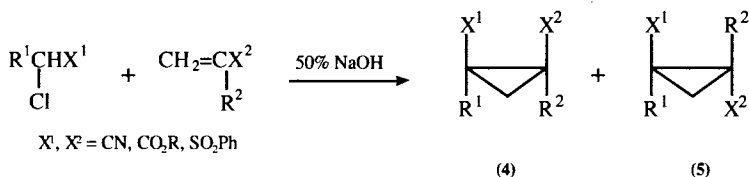
6.4.11 3-Nitroprop-1-enes

The nitroalkane (5.23 mmol), TBA-Cl (1.45 g, 5.23 mmol), $\text{KF}\cdot\text{H}_2\text{O}$ (1.99 g) in DMSO (5.2 ml) are stirred for 30 min at room temperature. The alkyne (7.85 mmol) is added and the mixture is stirred for a further 1 h. H_2O (50 ml) is added and the aqueous solution is extracted with Et_2O (3×50 ml). The extracts are washed with aqueous HCl (1M, 2×50 ml), brine (2×50 ml), dried (MgSO_4), and evaporated to yield the allylic nitro compound.

6.4.12 Vinylation of (*N*-benzylidene)glycynonitriles

The *N*-protected aminoacetonitrile $\text{RCH}(\text{N}=\text{CHPh})\text{CN}$ (5 mmol) is added to powdered NaOH (2.4 g) and TEBA-Cl (0.5 g, 2.2 mmol) and the alkyne (20 mmol) in DMSO (2 ml) and the mixture is stirred for 15 min at room temperature. The adduct is isolated as described in 6.4.11 [e.g. $\text{MeC}(\text{N}=\text{CHPh})(\text{CN})\text{CH}=\text{CHPh}$, 42%; $\text{MeC}(\text{N}=\text{CHPh})(\text{CN})\text{C}(\text{OEt})=\text{CH}_2$, 70%]. Addition of $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ (3.4 g) in aqueous EtOH (1:3, 40 ml) to the Michael adduct (9 mmol) and reflux for 1 h yields the α,β -unsaturated ketone (~80%).

The formation of cyclopropanes from π -deficient alkenes via an initial Michael-type reaction followed by nucleophilic ring closure of the intermediate anion (Scheme 6.26, see also Section 7.3), is catalysed by the addition of quaternary ammonium phase-transfer catalysts [46, 47] which affect the stereochemistry of the ring closure (see Chapter 12). For example, equal amounts of (4) and (5) ($\text{X}^1, \text{X}^2 = \text{CN}$) are produced in the presence of benzyltriethylammonium chloride, whereas compound (4) predominates in the absence of the catalyst. In contrast, α,β -unsaturated ketones or esters and α -chloroacetic esters [e.g. 48] produce the cyclopropanes (6) (Scheme 6.27) stereoselectively under phase-transfer catalysed conditions and in the absence of the catalyst. Phenyl vinyl sulphone reacts with α -chloroacetonitriles to give the non-cyclized Michael adducts (80%) to the almost complete exclusion of the cyclopropanes.

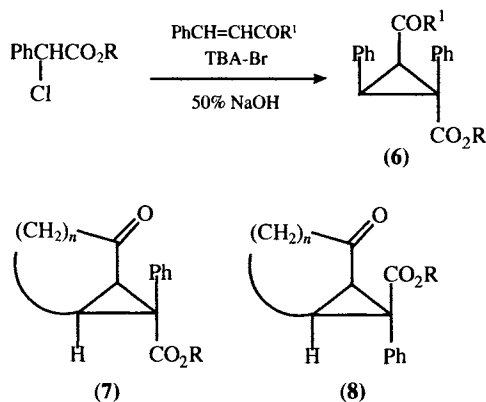


Scheme 6.26

Cyclohexenones preferentially produce the bicyclic compound (7) (Scheme 6.27, $n = 3$), whereas the reaction between cyclopentenone and *t*-butyl 2-chloro-2-phenylethanoate produces (7) and (8) ($n = 2$) in a *ca.* 2:1 ratio [49]. In a similar reaction, 3-acylcoumarins react with phenacyl bromide under mildly basic conditions to produce 4,5-benzo-3-oxa-2-oxobicyclo[4.1.0]heptanes [50].

The intermediate Michael adducts have been isolated from the reaction of α -chloro- α -nitroalkanes with α,β -unsaturated aldehydes, ketones, nitriles and esters

[51] and subsequent ring closure to give the nitrocyclopropanes (70%) can be conducted in a one-pot reaction analogous to that described in 6.4.13.A. The yield of the cyclopropane using this procedure is vastly superior to the standard method using sodium amide.



Scheme 6.27

6.4.13 Cyclopropanes

Method A (liquid:liquid conditions): The α,β -unsaturated ketone, ester, or nitrile (5 mmol) and the α -chloro ester (or nitrile) (5 mmol) in CH_2Cl_2 (25 ml) are stirred with TBA-Br or TEBA-Cl (5 mmol) in aqueous NaOH (50%, 10 ml) for 1–2 h at room temperature. The organic phase is separated, washed well with H_2O , dried (Na_2SO_4) and evaporated. The residue is triturated with Et_2O (50 ml) and the filtered solution is evaporated to yield the cyclopropane.

Method B (solid:liquid conditions): The α,β -unsaturated ester (25 mmol) and the α -chloro ester (25 mmol) are added to K_2CO_3 (6.9 g) and TEBA-Cl (0.3 g, 1.3 mmol) in DMF (10 ml) and the mixture is stirred at room temperature until the reaction is complete, as shown by TLC analysis (*ca.* 24 h). The mixture is then poured into H_2O (50 ml) and extracted with Et_2O (2×25 ml). The extracts are washed well with H_2O , dried (CaCl_2), and evaporated to yield the cyclopropane (40–50%).

6.4.14 Cyclopropanation of 3-acylcoumarins

Aqueous NaOH (4%, 4 ml) is added to the 3-acylcoumarin (1 mmol), phenacyl bromide (0.2 g, 1 mmol) and Aliquat (10 mg, 0.02 mmol) in PhH (4 ml) at 25°C and the mixture is stirred for 30 min and then poured into ice/ H_2O (50 ml). The aqueous mixture is neutralized with conc. HCl and extracted with CHCl_3 (3×20 ml). The extracts are washed with H_2O , aqueous Na_2CO_3 (sat. soln.), and H_2O , dried (Na_2SO_4), and evaporated to yield the bicyclo[4.10]heptane derivative.

α -Chloroacetonitriles, formed *in situ* from phenylacetonitriles under strongly basic conditions in carbon tetrachloride, react with acrylonitrile in a one-pot reaction

to produce the cyclopropane [52]. Although 2-aryl-2-chloroalkanonitriles, ArCCl(R)CN , can be isolated, 2-chloro-2-phenylacetonitrile ‘dimerizes’ under the basic conditions in the absence of a carbanionic trap to produce 1,2-dicyano-1,2-diphenylethene [52, 53].

6.4.15 α -Chlorophenylacetonitriles

The phenylacetonitrile (20 mmol) in CCl_4 (15 ml) is stirred with TEBA-Cl (50 mg, 0.22 mmol) in aqueous NaOH (50%, 15 ml) for 1.5 h at 20°C. Fractional distillation yields the α -chloro derivative $[\text{PhCHCl(R)CN}]$: R = Me, 78%; Et, 70%. The corresponding reactions starting from $\text{PhCH(NR}_2\text{)CN}$ produces $\text{PhCCCl}_3(\text{NR}_2)\text{CN}$ [R = Me, 36%; R = $-(\text{CH}_2)_5$, 43%].

Phase-transfer catalytic conditions provide an extremely powerful alternative to the use of alkali metal hydrides for the synthesis of cyclopropanes via the reaction of dimethyloxosulphonium methylides with electron-deficient alkenes [e.g. 54–56]; reaction rates are increased *ca.* 20-fold, while retaining high yields (86–95%). Dimethylphenacylsulphonium bromide reacts in an analogous manner with vinylsulphones [57] and with chalcones [58] and trimethylsulphonium iodide reacts with Schiff bases and hydrazones producing aziridines [59].

6.4.16 Cyclopropanes from dimethyloxosulphonium methylide

$\text{Me}_3\text{SO}^+\text{I}^-$ (2.2 g, 10 mmol) is added to the α,β -unsaturated ketone (10 mmol), KOH (5.6 g) and TEBA-Cl (10 mg, 0.04 mmol) in DMSO (20 ml) and the mixture is stirred at room temperature for *ca.* 1.5 h and then poured into H_2O (75 ml). The aqueous mixture is extracted with Et_2O (3×35 ml) and the extracts are dried (MgSO_4) and evaporated to yield the cyclopropane (86–90%).

6.4.17 Benzoylcyclopropanes from dimethylphenacylsulphonium bromide

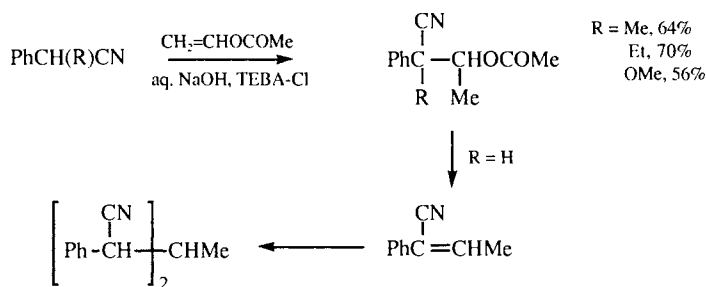
Aqueous NaOH (50%, 4 ml) is stirred with the electron-deficient alkene (10 mmol) and $\text{PhCOCH}_2\text{SMe}_2^+\text{Br}^-$ (2.6 g, 10 mmol), in CH_2Cl_2 (6 ml) for *ca.* 30 min before TEBA-Cl (0.2 g, 0.9 mmol) is added. The mixture is stirred at room temperature for 2–3 h and H_2O (50 ml) is then added. The organic phase is separated, washed well with H_2O and brine, dried (Na_2SO_4), and evaporated to yield the cyclopropane derivative (55–87%).

6.4.18 Aziridines from trimethylsulphonium iodide

$\text{Me}_3\text{S}^+\text{I}^-$ (20.4 g, 0.1 mol) is added to the imine or hydrazone (0.1 mol), TBA- HSO_4 (0.51 g, 1.5 mmol) in CH_2Cl_2 (100 ml) and aqueous NaOH (50%, 10 ml) and the mixture is stirred at 50°C for 2 h and then poured onto ice (100 g). The organic phase is separated, washed well with H_2O , dried (MgSO_4), and evaporated to yield the aziridine [e.g. 94% from PhCH=NPh ; 84% from $4\text{-MeOC}_6\text{H}_4\text{CH=N(4-MeOC}_6\text{H}_4\text{)}$; 92% from $2,4\text{-(O}_2\text{N)}_2\text{C}_6\text{H}_3\text{NHN=CHMe}$; 87% from $2,4\text{-(O}_2\text{N)}_2\text{C}_6\text{H}_3\text{NHN=CHPh}$].

The preparation of warfarin derivatives via the catalysed Michael-type reaction of 4-hydroxycoumarins with 4-arylbut-3-en-2-ones is achieved with a *ca.* 20-fold increase in reaction rate and a twofold increase in yields, compared with traditional methods [60]. Similarly, tetra-*n*-butylammonium fluoride catalyses the reaction of nitrotoluenes with α,β -unsaturated esters under mild solid:liquid two-phase conditions [14] with increased yields, compared with those observed in the absence of the catalyst.

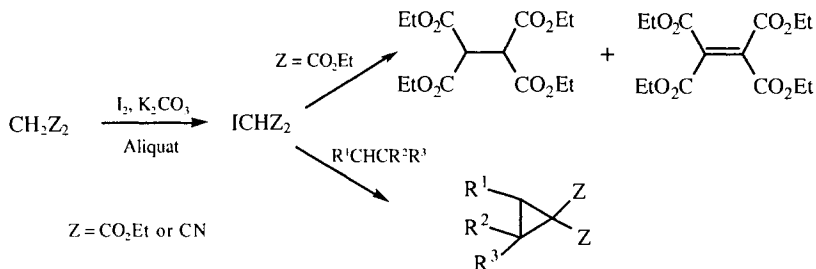
Although not a Michael acceptor, vinyl acetate reacts with a range of carbanions under phase-transfer catalytic conditions [61]. 1:1 Adducts are obtained from 1-cyano-1-phenylalkanes, but phenylacetonitrile produces a 2:1 adduct with loss of acetic acid (Scheme 6.28). The major product (40%) isolated from the reaction with diphenylmethyl cyanide is 1,2-dicyano-1,1,2,2-tetraphenylethane.



Scheme 6.28

6.4.19 3-Cyano-3-propyl acetates

Aqueous NaOH (50%, 5 ml) is added to the phenylacetonitrile (0.1 mol) and TEBA-Cl (0.1 g, 0.44 mmol) in MeCN (15 ml) at 15°C, followed by the dropwise addition of $\text{CH}_2=\text{CHOCOMe}$ (10.4 g, 0.12 mol). The mixture is stirred for 1.5–2 h at room temperature and then poured into H_2O (50 ml). The organic phase is separated, washed well with H_2O until neutral, dried (MgSO_4), and fractionally distilled to yield the ester.



Scheme 6.29

In a rather remarkable reaction, methylene groups activated by two electron-withdrawing substituents react with non-activated alkenes under solid:liquid phase-transfer conditions in the presence of a molar equivalent of iodine to yield cyclopropane derivatives (Scheme 6.29) [62, 63]. The reaction fails, when the catalyst is omitted or if iodine is replaced by bromine or chlorine. The intermediate iodomethylene systems are unstable in the absence of the reactive alkene and 'dimerize' to produce, for example, ethane-1,1,2,2-tetracarboxylic esters and ethene-1,1,2,2-tetracarboxylic esters.

6.4.20 Cyclopropanes from *in situ* produced iodomethylene systems

The alkene (10 mmol) is added over 2 h to the methylene compound (15 mmol), K_2CO_3 (3.3 g), I_2 (3 g) and Aliquat (0.1 g, 0.2 mmol) in refluxing PhMe (10 ml). The mixture is cooled to room temperature, filtered, and evaporated. The residue is taken up in PhMe (10 ml) and the solution is washed well with aqueous $Na_2S_2O_3$ (10%), dried (Na_2SO_4), and evaporated to yield the cyclopropane (Table 6.20).

TABLE 6.20

Selected examples of cyclopropanes from non-activated alkenes and *in situ* produced iodomethylene compounds

Methylene compound	$R^1CH=CR^2R^3$			% yield
$CH_2(CO_2Et)_2$	$R^1 = H$	$R^2 = n-Bu$	$R^3 = H$	35
	$CH=CCl_2$	Me	Me	52
$CH_2(CN)_2$	H	H	Ph	47
	H	Me	Ph	62
	$CH=CCl_2$	Me	Me	55

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6.5 OTHER C–C BONDING REACTIONS

Although the addition of quaternary ammonium salts to a two-phase Wittig reaction system normally has relatively little value, as phosphonium salts act as their own phase-transfer catalysts [e.g. 1], catalysis of the Wadsworth–Emmons (Wittig–Horner) reaction has been found to be advantageous both in the increase in yield of the alkenes and in the overall efficiency of the reaction under mild conditions [2–13]. Aliphatic aldehydes and ketones tend to undergo the Wadsworth–Emmons reaction less readily [see, e.g. 2] and, although the trend does not appear to be universal [5, 14], the configuration of the alkenes appears to depend to some extent on the quaternary ammonium salt used: chlorides give *ca.* 50:50 mixtures of *E*- and *Z*-isomers, whereas bromides and iodides produce *E:Z* ratios of *ca.* 80:20 [4]; benzothiazolylmethylphosphonates are reported to give the *E*-isomers exclusively [13]. The choice of the ammonium cation has little effect on the ratio. Solid:liquid two-phase systems are effective [10, 12], although, again, it has been suggested that the quaternary ammonium salt is not absolutely required [15] and unwanted phosphorus-containing by-products, e.g. $(\text{EtO})_2\text{POCR}^1=\text{CHR}^2$, may be formed particularly when $\text{R}^1 = \text{CN}$ [10]. The catalysed Wadsworth–Emmons reaction has been employed with success for the synthesis of ketene thioacetals [6, 8].

The use of polymer-supported quaternary ammonium salts to catalyse the Wadsworth–Emmons reaction produces acceptable yields from both aromatic and aliphatic aldehydes and ketones [16].

Although of little general use under ‘normal’ Wittig conditions, tetra-*n*-butylammonium iodide aids the reaction between polymer-bound benzylphosphonium salts and aromatic aldehydes with yields generally >90% [17].

6.5.1 Wittig reaction with polymer-bound phosphonium salts

Aqueous NaOH (50%, 3 ml) is stirred with polymer-bound benzylphosphonium salt (\equiv 1.5 mmol), aryl aldehyde (1 mmol), and TBA-I (11 mg, 0.03 mmol) in CH_2Cl_2 (10 ml) at 20°C for 4–16 h. The polymer is removed by filtration, and the filtrate is washed well with H_2O , dried (MgSO_4), and evaporated to yield the stilbene [e.g. $\text{PhCH}=\text{CHPh}$ (16 h), 92%; 4- $\text{MeC}_6\text{H}_4\text{CH}=\text{CHPh}$ (16 h), 100%; 4- $\text{ClC}_6\text{H}_4\text{CH}=\text{CHPh}$ (4 h), 97%].

6.5.2 Wadsworth–Emmons reactions (Table 6.21)

Method A: The phosphonate (25 mmol) and the aldehyde or ketone (35 mmol) are added with stirring at room temperature to TBA-I or TBA-Br (0.27 mmol) in aqueous NaOH (50%, 20 ml) and CH_2Cl_2 (35 ml). On completion of the reaction (the exothermic reaction with the cyano and ethoxycarbonyl compounds is complete after *ca.* 15 min), the organic

TABLE 6.21

Selected examples of the phase-transfer catalysed Wadsworth–Emmons reaction

Phosphonate	Aldehyde/ketone	Reaction conditions	% yield of alkene
(EtO) ₂ POCH ₂ CN	MeCHO	6.5.1.A/15 min/rt	51 ^a
	C ₆ H ₁₃ CHO	6.5.1.D	75 ^b
	PhCHO	6.5.1.A/15 min/rt	77 ^c
	PhCHO	6.5.1.C/24 h/100°C	49 ^d
	4-ClC ₆ H ₄ CHO	6.5.1.D	83 ^e
	Me ₂ CO	6.5.1.A/15 min/rt	62
	C ₉ H ₁₉ COMe	6.5.1.D	95 ^f
	PhCOMe	6.5.1.D	90 ^g
(EtO) ₂ POCH ₂ CO ₂ Et	MeCHO	6.5.1.A/15 min/rt	54 ^e
	C ₈ H ₁₇ CHO	6.5.1.D	64 ^e
	PhCHO	6.5.1.A/15 min/rt	56 ^e
	PhCHO	6.5.1.C/24 h/100°C	60 ^h
	4-ClC ₆ H ₄ CHO	6.5.1.D	97 ^e
(EtO) ₂ POCH ₂ SMe	PhCHO	6.5.1.B/1 h/reflux	59 ^h
(EtO) ₂ POCH ₂ SPh	PhCHO	6.5.1.B/1 h/reflux	81 ⁱ
	4-Me ₂ NC ₆ H ₄ CHO	6.5.1.B/2 h/reflux	40 ^j
(EtO) ₂ POCH ₂ SOPh	PhCHO	6.5.1.B/30 min/rt	54 ^k
	4-ClC ₆ H ₄ CHO	6.5.1.B/4 h/rt	57
	4-MeOC ₆ H ₄ CHO	6.5.1.B/4 h/reflux	48
(EtO) ₂ POCH ₂ SO ₂ Me	PhCHO	6.5.1.B/3 h/rt	85 ^e
	4-ClC ₆ H ₄ CHO	6.5.1.B/2 h/rt	71 ^e
	4-MeOC ₆ H ₄ CHO	6.5.1.B/2 h/rt	73 ^e
(EtO) ₂ POCH(SR) ₂	PhCHO	6.5.1.B/30 min/rt	88
(EtO) ₂ POCH ₂ SePh	PhCHO	6.5.1.B/2 h/rt	63 ^l
(EtO) ₂ POCH ₂ (2-pyridyl)	PhCHO	6.5.1.A/1 h/rt	71 ^e
	PhCH=CHCHO	6.5.1.A/1 h/rt	68 ^e
(EtO) ₂ POCH ₂ (2-BT) ^m	EtCHO	6.5.1.A/1 h/rt	69 ^e
	CH ₂ =CHCH ₂ CHO	6.5.1.A/1 h/rt	60 ^e
	PhCHO	6.5.1.A/1 h/rt	68 ^e

^a Z:E ratio 39:61. ^b Z:E ratio 1:3. ^c Z:E ratio 24:76. ^d + 30% PhCH=C(CN)PO(OEt)₂. ^e 100% E-isomer. ^f Z:E ratio 1:2. ^g 83% using TBA-Cl and KF·2H₂O in MeCN. ^h E:Z ratio 87:13. ⁱ E:Z ratio 48:52. ^j E:Z ratio 4:1. ^k E:Z ratio 83:17. ^l E:Z ratio 1:9. ^m BT = benzothiazole.

phase is separated, washed with H₂O (5 ml), dried (MgSO₄), and evaporated to yield the alkene.

Method B: The phosphonate (10 mmol) and aldehyde (10 mmol) in CH₂Cl₂ (5 ml) are added to TEBA-Cl (0.2 g, 0.87 mmol) in CH₂Cl₂ (20 ml) and aqueous NaOH (50%, 15 ml). The mixture is stirred at room temperature or heated under reflux and, on completion of the reaction, the product is worked up as described in 6.5.2.A.

Method C (solid:liquid conditions): KF·2H₂O (4.7 g, 50 mmol), TBA-Br (50 mg, 1.56 mmol), the phosphonate (10 mmol) and the aldehyde (10 mmol) in DMF (25 ml) are heated at 100°C for 24 h. On completion of the reaction, the mixture is poured into an excess of H₂O, extracted with CH₂Cl₂ and the organic extracts are worked up as described in 6.5.2.A.

Method D (using polymer supported catalyst): Amberlyst A-26 (OH form) (5 g) is shaken

in MeOH (25 ml) with the phosphonate (10 mmol) for *ca.* 2 h. The resin is collected, washed well with THF, and dried. The resin (equivalent to 5.6 mmol) and aldehyde or ketone (3.5 mmol) are stirred in THF (10 ml) for *ca.* 1 h. When the reaction is complete, as shown by GLC analysis, the resin is removed and the filtrate is evaporated to yield the alkene.

6.5.3 Ketene thioacetals

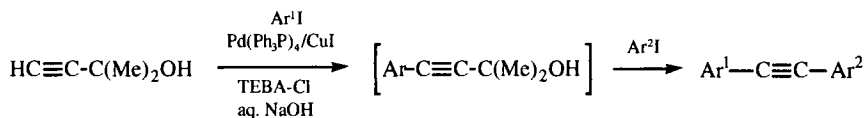
The phosphonate, e.g. (MeO)₂POCH(SMe)₂, (10 mmol) and the aryl aldehyde (10 mmol) in CH₂Cl₂ (5 ml) are added to aqueous NaOH (50%, 10 ml), TEBA-Cl (0.1 g, 0.43 mmol) in CH₂Cl₂ (5 ml) and the mixture is stirred for 30 min at room temperature. The organic phase is separated, washed well with aqueous NH₄Cl, dried (MgSO₄), and evaporated to yield the ketene thioacetal (>80%).

Cyanoalkenes are obtained from the catalysed reaction of carbonyl compounds and *O*-ethyl *S*-cyanomethyldithiocarbonates, or diethyl *S*-cyanomethylphosphorothionates, under basic conditions [11]. The reaction is analogous to the Darzens reaction (see Section 6.3) and probably proceeds via an intermediate thiirane.

6.5.4 Cyanoalkenes

Aqueous NaOH (50%, 13 ml) is added to the EtO.CS.SCH(R)CN, or (EtO)₂POSCH(R)CN, (20 mmol), the carbonyl compound (22 mmol), and Aliquat (0.2 g, 0.5 mmol) in MeCN (3 ml) at 0°C and the mixture is stirred initially for 5 min at 0°C and then 2 h at room temperature. The mixture is then poured into H₂O (300 ml) and the aqueous mixture is extracted with Et₂O (4 × 50 ml). The ethereal extracts are washed well with brine, dried (Na₂SO₄), and fractionally distilled to yield the cyanoalkene (45–70%).

Palladium-catalysed C–C bond formation under Heck reaction conditions, which normally requires anhydrous conditions and the presence of copper(I) salts, is aided by the addition of quaternary ammonium salts. It has been shown that it is frequently possible to dispense with the copper catalyst and use standard two-phase reactions conditions [e.g. 18, 19]. Tetra-*n*-butylammonium salts catalyse the palladium-catalysed reaction of iodoarenes with alkynes to yield the arylethynes in high yield [20, 21], whereas the reaction with 3-methylbut-1-yn-3-ol (Scheme 6.30) provides a route to diarylethynes [22]. Diarylethynes are also formed from the reaction of an iodoarene with trimethylsilylethyne [23]. Iodoalkynes react with α,β -unsaturated ketones and esters to produce the conjugated yne-eneones [19].



Scheme 6.30

6.5.5 1-Arylalk-1-ynes

Method A: The iodoarene (24.5 mmol) in PhH (40 ml) is added to TEBA-Cl (0.18 g, 0.86 mmol), CuI (0.25 g) and $(\text{Ph}_3\text{P})_4\text{Pd}$ (0.99 g) and the mixture is saturated with $\text{MeC}\equiv\text{CH}$ at 5°C. The mixture is stirred with degassed aqueous NaOH (2.5 M, 44 ml) under an atmosphere of $\text{MeC}\equiv\text{CH}$ at room temperature until the reaction is complete, as shown by TLC analysis (*ca.* 7 h). The mixture is then stirred at room temperature with aqueous NH_4Cl (sat. soln, 100 ml) for 1 h and extracted with *n*- C_6H_{14} (4×50 ml). The organic extracts are evaporated and the arylpropyne is isolated by chromatography.

Method B: $\text{Pd}(\text{OAc})_2$ (44.5 mg) and Ph_3P (0.105 g) in $\text{H}_2\text{O}:\text{MeCN}$ (1:10, 5 ml) are stirred with the alkyne (2 mmol), the aryl iodide (4 mmol), Et_3N (0.7 ml) and TBA- HSO_4 or TBA-Cl (2 mmol) in $\text{H}_2\text{O}:\text{MeCN}$ (1:10, 5 ml) at room temperature until the reaction is complete, as shown by GLC analysis. H_2O (10 ml) is added and the aqueous solution is extracted with Et_2O (3×30 ml). The dried (MgSO_4) extracts are evaporated to yield the arylalkyne.

6.5.6 Diarylethyne

Method A: $\text{CH}\equiv\text{CC}(\text{Me})_2\text{OH}$ (1.764 g, 21 mmol) and the iodoarene (21 mmol) in degassed PhH (15 ml) is added rapidly to TEBA-Cl (0.14 g, 0.6 mmol), CuI (0.19 g) and $(\text{Ph}_3\text{P})_4\text{Pd}$ (1.1 g). Degassed aqueous NaOH (5.5 M, 15 ml) is then added and the mixture is stirred at room temperature for 16–50 h. When the reaction is complete, as shown by TLC analysis, the second iodoarene (21 mmol) in degassed PhH (10 ml) is added and the mixture is stirred at 70–80°C for 40–50 h. Aqueous NH_4Cl (sat. soln, 100 ml) is added and the mixture is stirred at room temperature for 1 h and then extracted with PhH (4×50 ml). The organic extracts are evaporated and the diarylethyne isolated by chromatography [e.g. 2-thienyl $\text{C}\equiv\text{CPh}$, 80%; 2-thienyl $\text{C}\equiv\text{C}$ (2-pyridyl), 67%; 2-thienyl $\text{C}\equiv\text{C}(\text{benz}[b]\text{thien-2-yl})$, 45%; 2-thienyl $\text{C}\equiv\text{C}$ (2-thienyl), 75%; 2-thienyl $\text{C}\equiv\text{C}$ (2,5-thienyl) $\text{C}\equiv\text{C}$ (2-thienyl), 37% from 2-iodothiophene and 2,5-di-iodothiophene].

Method B: $\text{Me}_3\text{SiC}\equiv\text{CH}$ (0.98 g, 10 mmol), $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.6 g), CuI (0.16 g) and TEBA-Cl (0.12 g, 0.5 mmol) in degassed aqueous NaOH (2.5 M, 20 ml) are added to the iodoarene (5 mmol) in PhH (20 ml) under Ar and the mixture is stirred at 40°C for *ca.* 48 h. Aqueous NH_4Cl (sat. soln, 100 ml) is added and the mixture is stirred for a further 30 min. The aqueous mixture is extracted with Et_2O (4×35 ml) and the extracts are washed well with H_2O until the washings are neutral, dried (MgSO_4), and evaporated to yield the arylethyne (e.g. from PhI, 70%; from 2-iodothiophene, 91%).

6.5.7 Reaction of iodoalkynes with α,β -unsaturated carbonyl compounds

The α,β -unsaturated ketone or ester (0.3 mol), Na_2CO_3 (7.95 g) and TBA-Cl (8.334 g, 30 mmol) in DMF (5 ml) are stirred for 10 min at room temperature. $\text{Pd}(\text{OAc})_2$ (0.33 g, 1.47 mmol) is then added and the mixture is stirred for a further 5 min before the iodoalkyne (30 mmol) in DMF is added dropwise over 1 h. The mixture is then stirred for 3–6 h at room temperature until GLC analysis indicates the complete consumption of the alkyne. The volatile material is evaporated and Et_2O (150 ml) is added. The ethereal mixture is filtered through Celite, washed with H_2O (50 ml), dried (MgSO_4), and evaporated to yield the conjugate carbonyl system (50–60%).

As an alternative to the Ullmann reaction, haloarenes are coupled to form the biaryls using palladium acetate in the presence of a base and tetra-*n*-butylammonium bromide [24]. Yields are generally high (>70%) but dehalogenation of the haloarene may also occur as a side reaction.

6.5.8 Symmetrical biaryls

$\text{Pd}(\text{OAc})_2$ (90 mg, 0.4 mmol), TBA-Br (1.29 g, 4 mmol) and K_2CO_3 or Et_3N (8 mmol) are stirred in DMF (1 ml) with the bromoarene (8 mmol) at 115°C for 5 min. Me_2CHOH (0.6 ml) is then added and the mixture is stirred at 115°C for a further period. H_2O (10 ml) and Et_2O (10 ml) are added to the cooled mixture and the organic phase is separated, washed with H_2O (10 ml), dried (MgSO_4), and evaporated to yield the biaryl [e.g. Ar = 4-CNC₆H₄, 63% (no Me_2CHOH added, 6 h); 3-CNC₆H₄, 57% (6 h); 3-FC₆H₄, 86% (30 h); 3-ClC₆H₄ (from 3-ClC₆H₄I), 82% (8 h); 4-MeOC₆H₄ (from 4-MeOC₆H₄I), 80% (8 h); 4-O₂NC₆H₄, 31% (7 h); 2-CNC₆H₄, 86% (8 h); 2-MeOC₆H₄, 57% (6 h); 2,2'-bipyridyl, 95% (45 h)]

Reductive dimerization of substituted pyridines to yield bipyridyls by zinc is catalysed by nickel salts under phase-transfer catalytic conditions [25].

6.5.9 Trifluoromethyl-2,2'-bipyridyls

$\text{NiBr}_2(\text{PPh}_3)_2$ (2.23 g), Et_4NI (2.01 g, 10 mmol) and Zn (0.98 g) are stirred in degassed THF (20 ml) under Ar for 30 min. The 2-chloropyridine (10 mmol) in THF (10 ml) is added and the mixture stirred at 50°C for 24 h and then poured into aqueous NH_3 (2M, 100 ml). The mixture is filtered and the filtrate is extracted with CHCl_3 (2×100 ml). The extracts are washed with H_2O (2×50 ml), dried (MgSO_4), and evaporated to yield the 2,2'-bipyridyl [e.g. 4,4'-(CF₃)₂ derivative, 40%; 5,5'-(CF₃)₂, 20%; 4,4',5,5'-(CF₃)₄, 3%].

β -Arylation of acrylic esters yields the cinnamic esters (>90%) [18, 26], whereas α -aminocinnamic acids are obtained in moderate yields from iodoarenes and BOC-protected 2-aminoacrylates [27, 28]. 1,3- and 1,4-diiodobenzene yields mixtures of mono- and di-substituted arenes, but 1,2-diiodobenzene fails to react. The analogous reaction of ethyl cinnamate with iodoarenes gives ethyl *E*-3-aryl-3-phenylpropenoates as the major products [29]. When quaternary ammonium salts are used in the Heck-type reaction of iodoarenes with acrylic esters, the hydrogen sulphate salts tend to lead to lower conversions. However, it has been shown that the yields can be improved and be as good as those obtained when the reactions are catalysed by ammonium chlorides or bromides, when either molecular sieves are added [30], or when aqueous acetonitrile (1:10) is used instead of the dry solvent [31]. The reaction is also successful when conducted in water with no organic solvent. In addition to the normal Heck reaction, 2-bromobenzaldehydes undergo an unusual 'double' Heck reaction with methyl acrylate involving a deformylation reaction to produce 2-(methoxycarbonyl)ethylcinnamic esters [32] using essentially procedure 6.5.10.B in dimethylformamide.

The Heck reaction on polymer-bound iodoarenes is assisted by the addition of a catalytic amount of tetra-*n*-butylammonium bromide and has been employed in the synthesis of 4-carboxycinnamic esters and amides [33], and 4-aminosulphonylcinnamic esters [34]. It has also been reported that the presence of an equimolar equivalent of benzyltriethylammonium chloride aids the Pd(II)-mediated reaction of *N*-acyl-2-iodoanilines with vinylidene carbonate, which leads to *N*-acyl-2-hydroxyindolines providing a convenient route to the indoles (80–90%) [35]. The catalysed reaction of 2-hydroxy- and 2-tosylaminoiodobenzene with 1,2-dienes produces 1,2-dihydrobenzofurans and 1,2-dihydroindoles, respectively [36].

β -Phenylation of α,β -unsaturated ketones in high yield (75–85%), using the palladium catalysed reaction with phenylmercury(II) chloride or tetraphenyltin(IV), is promoted by tetra-*n*-butylammonium chloride [37].

6.5.10 Cinnamic esters

Method A: Ph₃P (0.26 g), the aryl iodide (10 mmol), and the acrylic ester (20 mmol) are added sequentially to NaHCO₃ (2.1 g), TBA-HSO₄ or TBA-Br (10 mmol) and crushed 4 Å molecular sieves (0.8 g) in MeCN (2 ml) and the mixture is stirred for 15 min at room temperature. Pd(OAc)₂ (0.11 g) is added and the mixture stirred for ca. 3.5 h at 60 °C. The mixture is cooled to room temperature, H₂O (25 ml) is added, and the aqueous solution is extracted with Et₂O (3 × 25 ml). Evaporation of the dried (MgSO₄) extracts yields the Heck adduct.

Method B: Pd(OAc)₂ (0.11 g) is added with stirring to the iodoarene (10 mmol), Ph₃P (0.26 g), CH₂=CHCO₂Me (20 mmol), K₂CO₃ (0.35 g) and TBA-HSO₄ or TBA-Br (10 mmol) in aqueous MeCN (1:10, 10 ml). The mixture is stirred for 2 h at 50 °C and the cinnamic ester is isolated using the procedure described in 6.5.10.A.

6.5.11 Arylation of 2-aminoacrylates

The iodoarene (0.38 mmol), the BOC-protected 2-aminoacrylic ester (0.54 mmol), Pd(OAc)₂ (2.6 mg, 0.011 mmol) TBA-Cl (0.11 g, 0.38 mmol) and NaHCO₃ (80 mg, 0.95 mmol) in DMF (5 ml) are stirred at 85 °C for 16 h. H₂O (25 ml) is then added and the aqueous solution is extracted with CH₂Cl₂ (3 × 15 ml). The extracts are washed with water (2 × 15 ml), dried (Na₂SO₄), and evaporated to yield the aminocinnamic ester ArCH=C(NHBOC)CO₂CH₂Ph [e.g. Ar = 2-FC₆H₄, 81%; 2-ClC₆H₄, 81%; 2-BrC₆H₄, 28%; 2-MeC₆H₄, 84%; 3-BrC₆H₄, 63%; 4-BrC₆H₄, 52% (+ 2% 1,4-C₆H₄⁻); 3-IC₆H₄, 38% (+ 20% 1,3-C₆H₄⁻); 4-IC₆H₄, 21% (+ 22% 1,4-C₆H₄⁻). Using 5.8 mg Pd(OAc)₂ with 1,3- and 1,4-I₂C₆H₄, the disubstituted arene is the major product].

6.5.12 Phenylation of α,β -unsaturated ketones (Table 6.22)

TBA-Cl (95 mg, 0.34 mmol), PdCl₂* (30 mg) and PhHgCl or Ph₄Sn (5.14 mmol) in aqueous HCl (3M, 4 ml) are added with stirring to the ketone (3.42 mmol) in CH₂Cl₂ (6.5 ml) at room temperature. The mixture is stirred until the reaction is complete, as shown by TLC analysis, and then washed with aqueous Na₂S₂O₄ (10%, 2 × 15 ml) and H₂O (2 × 15 ml), dried (Na₂SO₄), and evaporated. The crude product is purified by chromatography from silica. (*There is little advantage in using preformed TBA-PdCl₃.)

TABLE 6.22
Phenylation of α,β -unsaturated ketones

$R^1CH=CHCOR^2$	Reaction conditions	% yield of $PhCHR^1CH_2COR^2$	
		With $PhHgCl$	With Ph_4Sn
$R^1 = Ph \quad R^2 = Me$	6.5.11/5 h	85	88
$Ph \quad Ph$	6.5.11/14 h	78	75
$-(CH_2)_3-$	6.5.11/24 h	80	60

1-Alkynes react with haloethenes [38] to yield but-1-en-3-yne (55–80%), when the reaction is catalysed by Cu(I) and Pd(0) in the presence of a quaternary ammonium salt. The formation of pent-1-en-4-yne, obtained from the Cu(I)-catalysed reaction of equimolar amounts of alk-1-yne and allyl halides, has greater applicability and versatility when conducted in the presence of a phase-transfer catalyst [39, 40] although, under strongly basic conditions, 5-arylpent-1-en-4-yne isomerize. Symmetrical 1,3-diynes are produced by the catalysed ‘dimerization’ of terminal alkynes in the presence of Pd(0) and a catalytic amount of allyl bromide [41]. No reaction occurs in the absence of the allyl bromide, and an increased amount of the bromide also significantly reduces the yield of the diyne with concomitant formation of an endiyne. The reaction probably involves the initial allylation of the ethynyl carbanion and subsequent displacement of the allyl group by a second ethynyl carbanion on the Pd(0) complex.

6.5.13 But-1-en-3-yne

The haloethene (90 mmol) and the 1-alkyne (90 mmol) are added rapidly to TEBA-Cl (0.2 g, 0.9 mmol), CuI (0.17 g) and $(Ph_3P)_4Pd$ (0.49 g) in degassed PhH (25 ml). Degassed aqueous NaOH (10%, 100 ml) is added and the mixture is stirred at room temperature for 16 h. The mixture is diluted with H_2O (100 ml) and extracted with Et_2O (3×50 ml). The organic extracts are washed well with aqueous NH_4Cl (sat. soln) and then H_2O until the washings are neutral. The product, obtained on evaporation of the organic solution, is purified by chromatography from silica.

6.5.14 Pent-1-en-4-yne

Method A: The allyl halide (50 mmol) is added to the alk-1-yne (50 mmol), TBA-Cl (1.39 g, 5 mmol), CuI (0.5 g) and K_2CO_3 (10.35 g) in DMF (10 ml) under N_2 and the mixture is stirred at room temperature ($40^\circ C$ in the case of $PhC\equiv CH$) for 16–24 h (4 h in the case of $PhC\equiv CH$). Et_2O (50 ml) is added and the filtered solution is washed well with brine, dried ($MgSO_4$), and evaporated to yield the product, which is purified by flash chromatography on silica.

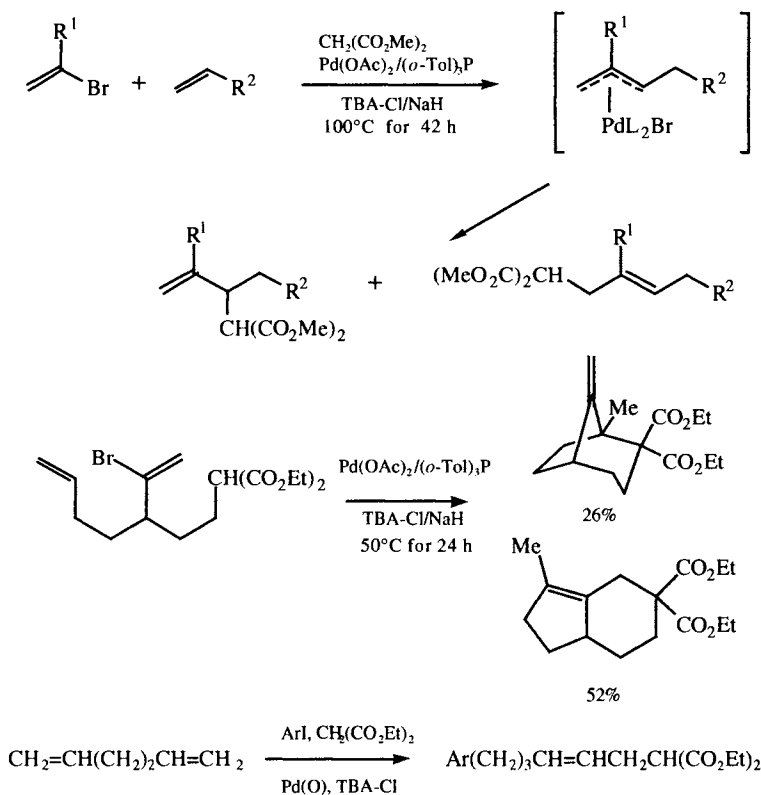
Method B: The allyl bromide (2.5 mmol) is added to the alk-1-yne (2 mmol), Aliquat (53 mg, 0.13 mmol), CuCl (50 mg) in degassed CH_2Cl_2 (4 ml) and aqueous NaOH (30%, 2 ml) under N_2 and the mixture is stirred at room temperature for 24–50 h. The mixture is evaporated and the residue taken up in $n-C_5H_{12}$. The filtered solution is evaporated to yield the enyne [e.g. *n*-

$\text{BuC}\equiv\text{CCH}_2\text{CH}=\text{CH}_2$, 73%; $n\text{-PrCH}(\text{Me})\text{C}\equiv\text{CCH}_2\text{CH}=\text{CH}_2$, 60%; $\text{PhC}\equiv\text{CCH}_2\text{CH}=\text{CH}_2$ 66% with $\text{PhC}\equiv\text{CCH}=\text{CH}=\text{CH}_2$ (6%) and $\text{PhCH}=\text{C}=\text{CHCH}=\text{CH}_2$ (17%).

6.5.15 1,3-Diynes

$\text{Pd}(0)(\text{PhCH}=\text{CHCOCH}=\text{CHPh})_2$ (56 mg, 1 mmol) is added to the 1-alkyne (20 mmol), TBA-Br (0.64 g, 2 mmol), $\text{CH}_2=\text{CHCH}_2\text{Br}$ (0.19 g, 1.6 mmol) and aqueous NaOH (50%, 10 ml). The mixture is stirred under N_2 for 24 h at room temperature and the organic phase is then separated and evaporated. The residue is taken up in $n\text{-C}_6\text{H}_{14}$, washed well with brine, dried (MgSO_4), and evaporated to yield the 1,3-diyne (e.g. from $\text{PrC}\equiv\text{CH}$, 80%; $\text{BuC}\equiv\text{CH}$, 85%; $\text{C}_5\text{H}_{11}\text{C}\equiv\text{CH}$, 90%; $\text{C}_6\text{H}_{13}\text{C}\equiv\text{CH}$, 90%).

The consecutive reaction of vinyl halides and alkenes with activated methylene systems [42] in the presence of a palladium catalyst and phase-transfer catalyst results from the addition of the methylene carbanion with the initially formed Heck product (Scheme 6.31); an intramolecular version of the reaction leads to the formation of bicycloalk-1-enes (Scheme 6.31) [42]. The analogous combined coupling reaction of iodoarenes and activated methylene compounds with non-conjugated dienes under similar conditions forms the monoalkene (Scheme 6.31) [43].



Scheme 6.31

6.5.16 Consecutive C–C bond formation leading to C-substituted malonic esters

$\text{CH}_2(\text{CO}_2\text{Et})_2$ (3.2 g, 20 mmol) is added dropwise with stirring under Ar at room temperature to NaH (0.48 g) and TBA-Cl (5.55 g, 20 mmol) in DMF (35 ml). $\text{Pd}(\text{OAc})_2$ (1.12 g) and (*o*-Tol) $_3\text{P}$ (3 g) are added, followed by the alkene (10 mmol) and vinyl halide (10 mmol). The degassed mixture is heated at 50–100 °C for 24–48 h in a vessel sealed under reduced pressure. The cooled mixture is filtered through silica, evaporated, and the product is purified by flash chromatography.

6.5.17 1,1-Disubstituted 7-arylhept-3-enes $[\text{Ar}(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{CHXY}]$

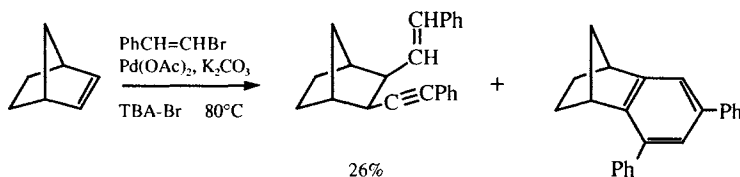
Na_2CO_3 (0.13 g), TBA-Cl (0.15 g, 0.55 mmol), $\text{Pd}(0)(\text{PhCH}=\text{CHCOCH}=\text{CHPh})_2$ (14 mg, 0.025 mmol) and $\text{CH}_2=\text{CH}(\text{CH}_2)_2\text{CH}=\text{CH}_2$ (85 mg, 1 mmol) are added to the iodoarene (0.5 mmol) and the activated methylene compound (CH_2XY) (1 mmol) in DMSO (1 ml) and the mixture is stirred at 80 °C under N_2 until all of the iodoarene is consumed, as shown by GLC analysis. Et_2O (20 ml) is added and the filtered ethereal solution is washed well with aqueous NH_4Cl (sat. soln), dried (MgSO_4), and evaporated to yield the hept-3-ene.

A simple tandem Michael addition of cyanide ion with alkylation on π -deficient alkenes has been effected on diethyl 1-methylpropylidenecyanoacetates and benzylidenemalonates using benzyltriethylammonium chloride to yield 2-alkyl-2,3-dicyanopropanoates and the analogous 2-ethoxycarbonyl derivatives [44].

6.5.18 Tandem Michael addition and alkylation of acrylic esters

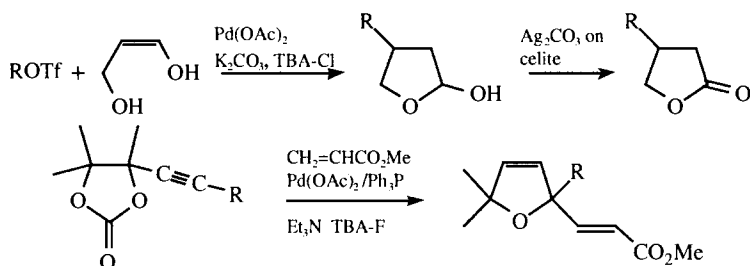
$\text{PhCH}=\text{C}(\text{CO}_2\text{Et})_2$ or $\text{EtCH}(\text{Me})\text{CH}=\text{C}(\text{CN})\text{CO}_2\text{Et}$ (10 mol) and the haloalkane (20 mmol) in CHCl_3 (10 ml) are stirred with NaCN (15 g, 20 mmol) and TEBA-Cl (1 g, 4 mmol) in H_2O at ca. 40 °C. When the reaction is complete, the mixture is poured into H_2O , neutralized with aqueous HCl (1M) (**Caution:** HCN), and extracted with CH_2Cl_2 (3 \times 15 ml). The extracts are washed with aqueous HCl (1%, 25 ml), dried (Na_2SO_4), and evaporated to yield the adduct [e.g. $\text{PhCH}(\text{CN})\text{CH}(\text{R})(\text{CO}_2\text{Et})_2$: R = Me, 45%; PhCH_2 , 97%; $\text{CH}_2\text{CH}=\text{CH}_2$, 79% and $\text{EtCH}(\text{Me})\text{CH}(\text{CN})\text{C}(\text{CN})(\text{R})\text{CO}_2\text{Et}$: R = PhCH_2 , 81%; $\text{CH}_2\text{CH}=\text{CH}_2$, 87%].

Bicyclo[2.2.1]hept-2-enes react with β -bromostyrene to form 1:2 adducts; 2-(phenylethynyl)-3-(2-phenylethenyl)bicyclo[2.2.1]heptane and the ring-closed tricyclo compound are both isolated (Scheme 6.32) [45]. Comparison of these results should be with those of the reaction in the absence of the quaternary ammonium salt, where the major reaction pathway leads to 2:1 and 1:1 adducts [46].



Scheme 6.32

Optimum yields of β -vinyl- γ -butyrolactols from the Pd(II) promoted reaction of vinyl triflates with *Z*-but-2-en-1,4-diol (Scheme 6.33) are attained when tetra-*n*-butylammonium chloride is added [47]. The lactol is conveniently oxidized to the lactone with celite-supported silver carbonate. The corresponding arylbutyrolactols are obtained in high yield (70–80%) from an analogous reaction of iodoarenes with the enediol. The yields of 2-alkenyl-2,5-dihydrofurans, resulting from the Pd(0) catalysed reaction of cyclic alkynylcarbonates with acrylic esters via tandem C–C and C–O bond forming reactions, are enhanced by the presence of tetra-*n*-butylammonium fluoride (e.g. Scheme 6.33) [48].



Scheme 6.33

6.5.19 β -Substituted γ -butyrolactols

$\text{Pd}(\text{OAc})_2$ (5.8 mg, 0.026 mmol) in DMF (1 ml) is added to the triflate (0.86 mmol), but-2-en-1,4-diol (0.114 g, 1.29 mmol), K_2CO_3 (0.297 g) and TBA-Cl (0.24 g, 0.86 mmol) in DMF (2 ml) and the mixture is stirred under N_2 at 70° for *ca.* 3 h. EtOAc (25 ml) and H_2O (25 ml) are added and the organic phase is separated, washed well with H_2O , dried (Na_2SO_4), and evaporated to yield the lactol (75–90%).

The Gomberg coupling reaction of aryl diazonium salts with arenes is catalysed by quaternary ammonium salts [49]. Although yields are variable, they are generally >50% [49, 50]. When aromatic solvents other than benzene are used, the appropriate biaryls are produced, e.g. 4-chlorobenzenediazonium tetrafluoroborate reacts with chlorobenzene to produce the 2,4'-, 3,4'- and 4,4'-dichlorobiphenyls in a *ca.* 67:18:15 ratio.

6.5.20 Gomberg coupling reactions

Solid $\text{ArN}_2^+\text{BF}_4^-$ (10 mmol), AcOK (2 g), and TBA- HSO_4 , or TEBA-Cl (0.5 mmol) are stirred in PhH (100 ml) at room temperature for *ca.* 24 h. The reaction mixture is filtered and the filtrate is washed well with H_2O and brine, dried (Na_2SO_4), and evaporated to yield the biaryl, which is purified by chromatography from silica (e.g. 4-MeOC₆H₄Ph, 87%; 2-ClC₆H₄Ph, 60%; 2-BrC₆H₄Ph, 51%).

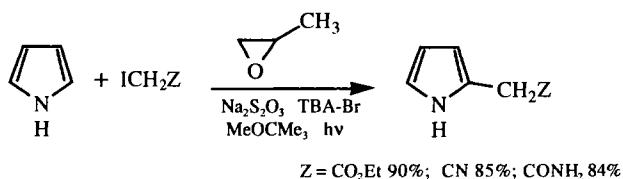
Palladium clusters [51], solubilized by tetra-*n*-alkylammonium salts, are effective in the Suzuki coupling of phenylboronic acid with bromoarenes to produce biaryls

(>80%) [52]. Similarly, diethyl 3-pyridylborane reacts with a range of halo-heteroarenes to produce 3-(heteroaryl)pyridines (60–85%) [53].

6.5.21 Suzuki-coupling reactions

The arylborane, or heteroarylborane (8 mmol), TBA-Br (1.28 g, 4 mmol), powdered KOH (11.8 g), the haloarene (12 mmol) and $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.46 g, 0.4 mmol) are refluxed in THF under N_2 for 8 h. EtOAc (100 ml) is added to the cooled mixture and the organic mixture is washed with brine (40 ml) and dried (MgSO_4). Evaporation under reduced pressure and chromatography from silica gives the biaryl system [e.g. 3-(2-pyridyl)pyridine, 85%; 3-(3-pyridyl)pyridine, 82%; 3-(5-methoxycarbonyl-2-pyridyl)pyridine, 63%; 3-(6-methoxy-2-pyridyl)pyridine, 77%; 3-(2-thienyl)pyridine, 75%].

A novel aromatic substitution reaction with electron-deficient radicals, which avoids the use of stannanes, is promoted by the addition of tetra-*n*-butylammonium bromide [54]. Iodoacetonitrile and iodoacetic esters react with pyrroles and indoles in good to high yield upon photolysis in the presence of 2-methyloxirane and sodium thiosulphate (Scheme 6.34).



Scheme 6.34

6.5.22 Radical substitution of pyrroles and indoles

The iodoalkane (1 mmol) and an excess of the heteroarene (5–15 mmol), $\text{Na}_2\text{S}_2\text{O}_3$ (0.16 g), 2-methyloxirane (0.3 g), and TBA-Br (32 mg, 0.1 mmol) are added to MeOCMe_3 (2 ml) in a Pyrex tube. The mixture is degassed under Ar at 0°C and photolysed for 36–48 h with a medium pressure Hanovia lamp. Et_2O (10 ml) is added to the mixture and the organic phase is separated, washed well with H_2O , dried (MgSO_4), and evaporated to yield the substituted heteroarene.

Aromatic aldehydes undergo a pinacol reaction when treated with hexamethyldisilane and tetra-*n*-butylammonium fluoride [55] using procedure 3.1.14.D.

Perfluoroalkyl cyanides react with nitromethane under basic conditions in the presence of benzyltriethylammonium chloride to give the 1-amino-1-perfluoroalkyl-2-nitroethenes (53–72%) [56].

Analogous to its reaction with carbonyl compounds (see 6.3.4), benzyltrimethylsilane undergoes a fluoride-induced nucleophilic substitution reaction on pyridine-1-oxides and quinoline-1-oxide to form 2-benzylpyridines (>70%) and 2-benzylquinoline (65%), respectively [57]. Allyltrimethylsilane reacts with pyridine-1-oxide to produce 2-propenylpyridine (56%).

$$\begin{array}{l} \text{RCH(OAc)}_2 \xrightarrow[\text{CHCl}_3, \text{TEBA-Cl, room temperature}]{50\% \text{ aq. NaOH}} \begin{array}{c} \text{RCHOAc} \\ | \\ \text{CCl}_3 \end{array} \xrightarrow{40-45^\circ\text{C}} \begin{array}{c} \text{RCHOH} \\ | \\ \text{CCl}_3 \end{array} \\ \text{ArCH}_2\text{Br} \xrightarrow[\text{CHBr}_3, \text{TEBA-Cl, 60}^\circ\text{C 15 min}]{\text{aq. NaOH}} \text{ArCH}_2\text{CBr}_3 \longrightarrow \text{ArCH}\equiv\text{CBr} \end{array}$$

Scheme 6.35

Aqueous NaOH (50%, 16 ml) is added dropwise to the $\text{RCH}(\text{OAc})_2$ (0.1 mol) and CHCl_3 (10 g) and TEBA-Cl (0.23 g, 1 mmol) at $5-10^\circ\text{C}$. The mixture is stirred at $<25^\circ\text{C}$ * for 1 h and then extracted with Et_2O (3×10 ml). The dried (MgSO_4) extracts are fractionally distilled to yield the trichloroalkyl acetate (e.g. $\text{R} = \text{Me}$, 72%; $\text{CH}_2=\text{CH}$, 61%; $\text{PhCH}=\text{CH}$, 62%) (*at $40-45^\circ\text{C}$, the alkanol is isolated after 4–6 h).

The benzyl bromide (50 mmol) in CHBr_3 (10 ml) is stirred with TEBA-Cl (0.23 g, 1 mmol) in aqueous NaOH (50%, 10 ml) at 60°C for 15 min. The organic phase is separated, washed well with H_2O , filtered through Florosil and evaporated to yield the (2,2,2-tribromoethyl)arene (55–75%). Extended reaction times (20–48 h) leads to the formation of the ethyne (e.g. Ar = Ph, 60%; 4-MeC₆H₄, 53%; 4-O₂NC₆H₄, 58%).

TBA-Br (10 mg, 0.03 mmol) is added to *N*-phenacylpyridinium bromide (0.56 g, 2 mmol) and alkyne (4 mmol) in CH₂Cl₂ (18 ml) and aqueous K₂CO₃ (50%, 18 ml) and the mixture is stirred at room temperature for *ca.* 8 h. The aqueous phase is separated and extracted with CH₂Cl₂ (4 × 20 ml) and the combined organic solutions are evaporated to yield the indolizine, which is purified by chromatography from silica.

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Preparation and Synthetic Applications of Carbenes

7.1 INTRODUCTION

An excellent comprehensive review of the factors which influence the generation of dihalocarbenes under phase-transfer catalytic conditions, and their relative stabilities and reactivities has been presented by Dehmlow [1].

Halocarbenes

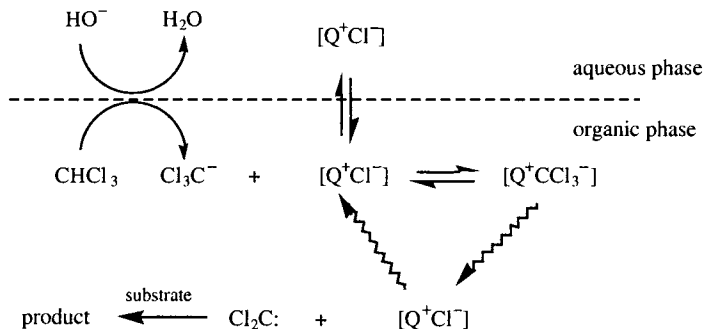
In one of the earliest studies of phase-transfer catalysed reactions, Makosza and his research group generated dichlorocarbene using a catalytic amount of benzyltriethylammonium chloride in an aqueous sodium hydroxide:chloroform two-phase system [2, 3] and it has become the standard method for the phase-transfer catalytic production of dichlorocarbene and related dihalocarbenes.

Compared with the 'classical' procedures, which employ chloroform and dry potassium *tert*-butoxide, Makosza's method is several magnitudes superior, in spite of the normally recognized requirements that the dichlorocarbene should be produced under totally anhydrous conditions. Several early reports of the reactions of dichlorocarbene, generated by Makosza's procedure, led to suggestions that the activity of the carbene was considerably greater than that of the 'classically' produced carbenes. This assumption was based on the overall higher yields of dichlorocyclopropanes derived from the reaction with alkenes, and upon the observation that weakly activated alkenes reacted with 'Makosza' carbenes, but not with the 'classically' produced carbenes. A consideration of the mechanism of formation of the carbenes under phase-transfer catalytic conditions exposes the fallacies in the assumptions.

As indicated in Chapter 1, the hydroxide ion is not readily transported into the organic phase, particularly when the benzyltriethylammonium ion is employed as the catalytic cation. Hence, the reaction of chloroform with the hydroxide ion must occur by an interfacial mechanism. The interfacial reaction initially produces the trichloromethyl anion, which immediately forms an effective ion-pair with the benzyltriethylammonium cation. Diffusion of the ion-pair into the bulk of the organic phase occurs, followed by a slow decomposition of the trichloromethyl anion

into dichlorocarbene. Cetyltrimethylammonium chloride and cetrimide can be used in place of benzyltriethylammonium chloride without loss of efficiency, and in specific cases, the small hard tetramethylammonium cation is also an effective catalyst.

Experimental evidence for the intermediate formation of the trichloromethyl anion is found in several examples where alkenes yield not only dichlorocyclopropanes, but also trichloromethylalkanes, as a result of electrophilic attack on the C=C bond (see Section 7.3) [4]. Generally, however, the dichlorocarbene is generated in the presence of a large excess of an alkene and immediate reaction produces the dichlorocyclopropanes in high yield (Scheme 7.1). In comparison, the formation of dichlorocarbene by the 'classical' reaction of chloroform and potassium *tert*-butoxide is instantaneous and, because of the short lifetime of the carbene, only a small proportion of the molecules have the opportunity to react with the alkenes. This is particularly accentuated when the alkene has a low reactivity. Additionally, there is a greater opportunity for carbenes to be solvolysed under the 'classical' conditions, compared with phase-transfer conditions where, when 50% aqueous sodium hydroxide is used, the percentage of water in the organic phase is negligible. It has been estimated that, in the catalysed reaction of dichlorocarbene with styrene, only 7% is hydrolysed, while 93% reacts with the reactive alkene. Predictably, the proportion of dichlorocarbene hydrolysed, compared with insertion into the C=C bond, increases with alkenes of lower reactivity [5]. The cycloaddition reactions are frequently exothermic and control of the temperature can sometimes be difficult, when Makosza's original procedure (7.1.1) is employed.



Scheme 7.1

Several variations of Makosza's procedure have been recorded using different catalysts. Generally, because of the need for the slow release of the dichlorocarbene in the presence of the reactive substrate, the 'weaker' catalysts are preferred. There seems, however, to be some advantage in the use of multisite ammonium salts, e.g. 2-benzylidene-*N,N,N',N',N'*-hexaethylpropane-1,3-diammonium dichloride, $\text{PhCH}=\text{C}(\text{CH}_2\text{NEt}_3)_2 \cdot 2\text{Cl}^-$, although yields and rate of reaction are not significantly better than those of Makosza's procedure [6, 7].

7.1.1 Makosza's procedure for the generation and reaction of dichlorocarbene

The reactive substrate (0.1 mol) and TEBA-Cl (0.23 g, 1 mmol) in CHCl_3 (47.5 g, 35 ml), which has been washed with H_2O to remove the EtOH stabilizer (see Section 7.5), are stirred (>800 r.p.m.) at 20°C and aqueous NaOH (50%, 80 ml) is added dropwise over a period of 1–2 h. The two-phase system is maintained at *ca.* 50°C for 2–3 h (weakly reactive substrates may require reaction times of over 100 h) and the mixture is then poured into H_2O (250 ml) and the organic layer is separated. The aqueous phase is washed with CHCl_3 (2×25 ml) and the combined organic solutions are dried (MgSO_4) and fractionally distilled.

7.1.2 Solid:liquid phase-transfer catalysed formation and reaction of dichlorocarbene

Powdered NaOH (20 g, 0.5 mol) or KOH (28 g, 0.5 mol) is added in one portion to the substrate (0.15 mol) and TEBA-Cl (0.34 g, 1.5 mmol) in CHCl_3 (100 ml) and the mixture is stirred (>800 r.p.m.) for *ca.* 15 min (for reactive substrates. A longer reaction period may be required for less reactive alkenes), with cooling if necessitated by the exothermic nature of the reaction. The reaction mixture is worked up as described in 7.1.1.

7.1.3 Makosza's procedure for the generation and reaction of dibromocarbene

Aqueous NaOH (50%, 100 ml) is added to the reactive substrate (0.2 mol) and TEBA-Cl (0.4 g, 1.7 mmol) in CHBr_3 (50.6 g, 0.4 mol) over a period of 10 min at 40 – 45°C (in some examples, small quantities of EtOH are also added). The mixture is stirred for 2.5–3 h [CH_2Cl_2 (20 ml) can be added if the mixture becomes viscous]. On completion of the reaction, the mixture is poured into H_2O (250 ml). The aqueous phase is separated, extracted with CH_2Cl_2 (2×25 ml) and the combined organic phases are washed with H_2O (2×25 ml), dilute HCl (2M, 25 ml) and H_2O (25 ml), dried (MgSO_4) and evaporated to yield the product.

That the formation of the trichloromethyl anion is an interfacial reaction is evident from the high stirring rate required to maintain reproducibly high yields (see Chapter 1). In many reported reactions, chloroform is used as the organic solvent, whereas in other examples it is used in a fourfold excess over the reactive substrate in dichloromethane. Benzene has also been used as the co-solvent but it reduces the rate of the reaction, probably because it is a poorer solvent for benzyltriethylammonium salts.

As indicated in Chapter 1, the use of concentrated (50%) aqueous sodium hydroxide inhibits the transfer of water into the organic phase and optimal yields are generally attained when the ratio of sodium hydroxide to reactive substrate is *ca.* 4 : 1 [8]. The use of solid sodium or potassium hydroxide enhances the rate of reaction with the reactive substrate [8, 9], but it has been suggested that, as the rate of hydrolysis of dichlorocarbene is also enhanced under the solid:liquid phase-transfer

conditions, the procedure may be less effective with extremely weak nucleophilic substrates.

Although other quaternary ammonium salts have been used, preference is generally given to Makosza's original conditions. Use of the more lipophilic tetra-*n*-butylammonium and trioctylmethylammonium salts has been reported [10–12], but there is no advantage in their use over the cheaper more hydrophilic salts, such as benzyltriethylammonium chloride. In several reactions, cetyltrimethylammonium bromide has been found to be an effective alternative catalyst for the benzyltriethylammonium salt. It is highly probable that the more lipophilic catalysts enhance the hydrolysis of chloroform by their more efficient transfer of the hydroxide anion into the organic phase. Trialkyl β -hydroxyethylammonium salts have been used in the generation of dichlorocarbene and they were originally reported to control the reaction of the carbene at selected sites of polyalkenes [13]. Additionally, it was claimed that a degree of asymmetric induction (see Chapter 12) in the reaction of the dichlorocarbene and styrene resulted from the use of the β -hydroxyethylammonium salt [13]. Both of these claims have been refuted. Thus, reactions of dichlorocarbene with polyenes have been shown to occur at all reaction sites, although there may be differences in the order of reactivity and it has also been established that purified samples of the dichlorocyclopropanes show no optical activity and it is probable that the activity arose from traces of the chiral catalyst or its decomposition products [5, 14].

The generation of the dichloromethane under phase-transfer conditions may be facilitated by the addition of a trace of ethanol. Alkoxide anions, generated under the basic conditions, are more readily transferred across the two-phase interface than are hydroxide ions (see Chapter 1). Although this process may result in the increased solvolysis of the chloroform, it also produces a higher concentration of the carbene in the organic phase and thereby increases the rate of formation of the cyclopropane derivatives from reactive alkenes.

Alternative procedures for the generation of dichlorocarbene and dibromocarbene under phase-transfer catalysed conditions are also available. Where the reactive substrate is labile under basic conditions, the thermal decomposition of solid sodium trichloroacetate or bromoacetate under neutral conditions in an organic solvent is a valuable procedure [10–12]. The decarboxylation is aided by the addition of a quaternary ammonium salt, which not only promotes dissolution of the trihaloacetate anion in the organic solvent, but also stabilizes the trihalomethyl anion. Under optimum reaction conditions, only a catalytic amount of the quaternary ammonium salt is required, as a large amount of the catalyst causes the rapid generation of the dichlorocarbene with resultant side reactions.

7.1.4 Phase-transfer catalysed reaction of dichlorocarbene generated from sodium trichloroacetate

Powdered $\text{CCl}_3\text{CO}_2\text{Na}$ (18.5 g, 0.1 mol) is added to the reactive alkene (0.05 mol) and Aliquat (0.5 g, 1 mmol) in CHCl_3 (50 ml) and the mixture is stirred at 80°C until the evolution of CO_2 ceases (*ca.* 5 h) during which time side reactions may cause the mixture

to become dark. H_2O (100 ml) is added and the organic phase is separated, filtered, dried (MgSO_4), and evaporated to yield the dichlorocyclopropane.

7.1.5 Phase-transfer catalysed reaction of dibromocarbene generated from sodium tribromoacetate

1,1-Dibromocyclopropanes are isolated following procedure 7.1.4 in which $\text{CCl}_3\text{CO}_2\text{Na}$ is replaced by $\text{CBr}_3\text{CO}_2\text{Na}$ (31.9 g, 0.1 mol).

Dichlorocarbene has also been generated by the reaction of tetrachloromethane, hexachloroethane, or bromotrichloromethane using 60% aqueous or solid potassium hydroxide in the presence of a tetra-*n*-butylammonium salt [15, 16]. Yields of insertion products are similar to those obtained by Makosza's procedure.

7.1.6 Phase-transfer catalysed reaction of dichlorocarbene generated from tetrachloromethane (or bromotrichloromethane)

Crushed KOH (33.7 g, 0.6 mol) and TBA-Br (1.6 g, 5 mmol) are added to CCl_4 (92.3 g, 0.6 mol) or CBrCl_3 (39.7 g, 0.2 mol) and the reactive substrate (0.1 mol) and the mixture is stirred at 95°C for *ca.* 6 h (6 h at 40°C for CBrCl_3). The product is isolated in a manner similar to that described in 7.1.1 [e.g. 14% dichlorocyclopropane derivative from $\text{PhC}(\text{Me})=\text{CH}_2$ and CCl_4 ; 63% + *ca.* 3% bromochlorocyclopropane, when CBrCl_3 is used].

Diiodocarbene is obtained from triiodomethane [17] by procedures analogous to those used for the production of dichloro- and dibromocarbene, and mixed dihalocarbenes have been generated under phase-transfer catalytic conditions from the appropriate trihalomethanes [17–24]. Bromochlorocarbene adducts cannot be produced effectively from either dibromochloromethane or bromodichloromethane, as halide exchange produces a mixture of $:\text{CCl}_2$, $:\text{CClBr}$ and $:\text{CBr}_2$ [25–27]. Similarly, a mixture of $:\text{CBr}_2$, $:\text{CBrI}$ and $:\text{CI}_2$ is produced by the base-catalysed α -elimination from dibromiodomethane or bromodiiodomethane and subsequent halide exchange [24]. It has been noted, however, that with the more nucleophilic alkenes, although the dibromocarbene adduct predominates when dibromiodomethane is used, it is the bromiodocyclopropane that is formed from bromodiiodomethane [24]. In order to obtain pure bromochlorocarbene adducts, the base-catalysed reaction of dibromomethane with trichloromethylbenzene is used [28].

Difluorocarbene cannot be generated (<1%) under liquid:liquid phase-transfer catalytic conditions [29] owing to the rapid hydrolysis of the carbene at the interface [30], although it has been indicated that it is possible to obtain low yields of 1,1-difluorocyclopropanes under solid:liquid conditions [1]. More successful is the reaction of dibromomethane and dibromodifluoromethane under basic conditions. It is assumed that the initially formed dibromomethyl anion is transported into the organic phase where an equilibrium reaction with dibromodifluoromethane produces the bromodifluoromethyl anion and, subsequently, the difluorocarbene [31].

7.1.7 Generation and reaction of diiodocarbene

Aqueous NaOH (50%, 50 ml) is added dropwise to CHCl_2 (30.2 g, 0.1 mol), the reactive substrate (0.1 mmol) and TEBA-Cl (0.5 g, 2.2 mmol) in CH_2Cl_2 (100 ml). The mixture is heated to 50°C for 3 h and then cooled to 0°C and acidified with dilute H_2SO_4 . The aqueous phase is separated and extracted with CH_2Cl_2 (2 × 25 ml). The combined organic solutions are dried (MgSO_4) and evaporated to yield the product.

7.1.8 Generation and reaction of chlorofluorocarbene

Method A: The reactive substrate (87 mmol), CHCl_2F (23.7 g, 0.23 mol), TMBA-Cl (0.8 g, 3 mmol) and aqueous KOH (50%, 30 ml) are cooled to 0°C and stirred, or mixed with a vibromixer, for ca. 30 min (or until the reaction is complete, as shown by GLC analysis). The product is isolated, as described in procedure 7.1.3.

Method B: The reactive substrate (0.2 mol), CHCl_2F (40 g, 0.39 mol), and TEBA-Cl (0.8 g, 3.5 mmol) in CH_2Cl_2 (50 ml) are mixed with aqueous NaOH (50%, 50 ml) at 30°C and stirred for 12 h. The reaction product is isolated, as described in procedure 7.1.3.

Method C for less reactive alkenes: The reactive alkene (0.1 mol), CHCl_2F (10.3 g, 0.1 mol), TMBA-Cl (0.4 g, 1.5 mmol) and aqueous NaOH (50%, 30 ml) are mixed at 0°C and the mixture is placed in a rotary autoclave and heated at 60°C for ca. 4 h. On completion of the reaction, the product is isolated, as described in procedure 7.1.3.

7.1.9 Generation and reaction of bromofluorocarbene

Method A: Aqueous NaOH (50%, 50 ml) is added dropwise to the reactive substrate (0.2 mol), CHBr_2F (39 g, 0.2 mol) and TEBA-Cl (0.8 g, 3.5 mmol) in CH_2Cl_2 (50 ml). The reaction is exothermic and refluxes spontaneously after 10 min. Heating is continued for a further 3 h and, finally, the mixture is stirred at room temperature for 1.5 h before being diluted with H_2O (2000 ml) and neutralized with HCl (10%). The aqueous phase is separated, extracted with CH_2Cl_2 (3 × 100 ml), and the combined organic solutions are washed well with aqueous NaHCO_3 (sat. soln.) and H_2O , dried (MgSO_4), and evaporated to yield the product.

Method B for reactive alkenes and labile cyclopropanes: The reagents from 7.1.9.A are mixed at 0°C and the mixture is then stirred at ca. 20°C for 3–4 h before being worked up as described in 7.1.9.A.

7.1.10 Generation and reaction of fluoroiodocarbene

CHFI_2 (28.6 g, 0.1 mol), the reactive organic substrate (0.3 mol) and TEBA-Cl (0.5 g, 2.2 mmol) in CH_2Cl_2 (30 ml) are stirred with aqueous NaOH (50%, 25 ml) for 4 h at 20°C. The reaction mixture is worked up as described in 7.1.9.A.

7.1.11 Generation and reaction of chloroiodocarbene

Aqueous NaOH (50%, 50 ml) is added dropwise with stirring to CHClI_2 (30.2 g, 0.1 mol), the reactive substrate (0.3 mol) and TEBA-Cl (0.5 g, 2.2 mmol) in CH_2Cl_2 (100 ml) at room temperature. The mixture is heated at 50°C for ca. 3 h and then diluted with H_2O (100 ml) and neutralized with H_2SO_4 (10%) at 0°C. The aqueous phase is separated and

extracted with CH_2Cl_2 (3×25 ml). The combined organic phases are washed with H_2O (25 ml), dried (MgSO_4), and evaporated to yield the product.

7.1.12 Generation and reaction of bromiodocarbene

The reactive substrate (0.1 mol), CHBrI_2 (10.3 g, 0.03 mol) TEBA-Cl (0.4 g, 1.7 mmol) in CH_2Cl_2 (50 ml) are stirred with aqueous NaOH (50%, 60 ml) for 17 h at room temperature. The reaction mixture is worked up as described in 7.1.11 to give a mixture of cyclopropanes (~20%) in which the 1-bromo-1-iodo derivative predominates over the 1,1-dibromo derivative by a ratio of *ca.* 2:1. The di-iodo compound is observed in only trace amounts (when CHBr_2I is used, the dibromo derivative predominates).

7.1.13 Generation and reaction of bromochlorocarbene

CH_2Br_2 (3.48 g, 20 mmol), PhCCl_3 (1.95 g, 10 mmol), the reactive substrate (10 mmol) and TBA- HSO_4 (0.2 g, 0.6 mmol) are stirred with aqueous KOH (60%, 7 ml) for 21 h at 25°C. The reaction mixture is diluted with H_2O (20 ml) and extracted with CH_2Cl_2 (3×10 ml). The extracts are washed with H_2O (15 ml), dried (MgSO_4), and evaporated to yield the product.

7.1.14 Generation and reaction of difluorocarbene

The reactive alkene (20 mmol), CBr_2F_2 (8.4 g, 40 mmol) and CH_2Br_2 (3.5 g, 20 mmol) are added to TBA- HSO_4 (0.34 g, 1 mmol) in aqueous KOH (60%, 25 ml) and the mixture is stirred at room temperature. The 1,1-difluorocyclopropane is isolated by a procedure analogous to that described 7.1.3.

Chloro(phenylthio)carbene [32] has been produced by the standard phase-transfer catalytic procedure from PhSCHCl_2 and trapped by alkenes (see Section 7.3), although the carbene is also prone to dimerization to give $[\text{PhS}(\text{Cl})\text{C}=\text{C}(\text{Cl})\text{SPh}]$. In a similar manner, phenylthiocarbene has been obtained from PhSCH_2Cl [33] and chloro(phenoxy)carbene from dichloro(phenoxy)methane [34]. Reaction of the analogous seleno derivatives produce the corresponding phenylselenocarbenes [35]. Chloro(methylthio)carbene is generated from dichloro(methylthio)methane [36].

7.1.15 Generation and reaction of chloro(phenylthio)carbene and phenylthiocarbene

Aqueous NaOH (50%, 15 ml) is stirred with the reactive substrate (50 mmol), TEBA-Cl (0.2 g, 0.87 mmol) and PhSCHCl_2 (7.76 g, 40 mmol) at 40–45°C for *ca.* 2 h. The reaction mixture is worked up, as described in 7.1.1.

Phenylthiocarbene can be produced by replacing the PhSCHCl_2 with PhSCH_2Cl (8.7 g, 55 mmol) in CH_2Cl_2 (20 ml). Use of a vibromixer has been found to have some advantage in this reaction.

7.1.16 Generation and reaction of chloro(phenylseleno)carbene and phenylselenocarbene

Method A (solid:liquid conditions): PhSeCH₂Cl (0.2 g, 1 mmol), the reactive organic substrate (1.25 mmol), Aliquat (8.1 mg, 0.02 mmol) and powdered KOH (0.5 g) are stirred at room temperature and then sonicated for 2 h, or until TLC analysis indicates the complete reaction of the substrate. The mixture is filtered through a pad of Celite, which is then washed well with *n*-C₆H₁₄. The combined organic solutions are dried (MgSO₄) and evaporated to yield the product.

Method B (liquid:liquid conditions): PhSeCHCl₂ (0.24 g, 1 mmol), the organic substrate (1.25 mmol), Aliquat (8.1 mg, 0.02 mmol) and aqueous NaOH (50%, 1.5 ml) are sonicated for 90 min at room temperature. H₂O (30 ml) is added and the aqueous mixture is extracted with CH₂Cl₂ (3 × 20 ml). The combined extracts are dried (MgSO₄) and evaporated to yield the product.

7.1.17 Generation and reaction of chloro(methylthio)carbene

Procedure 7.1.15 is used replacing the PhSCHCl₂ with MeSCHCl₂ (5.24 g, 40 mmol).

Non-halocarbenes

The base-induced elimination of hydrogen halides from 1-bromo-3-methylbuta-1,2-diene and 3-chloro-3-methylbut-1-yne under phase-transfer catalytic conditions [37–42] produces the transient dimethylvinylidene carbene (Me₂C=C=C:) which reacts with electron rich alkenes (see Section 7.3). A similar elimination of hydrogen bromide from 5-bromohexa-3-ene-1-yne in the presence of tetra-*n*-butylammonium iodide to produce 3-(propen-1-yl)vinylidene carbene (MeCH=CHCH=C=C:) is in competition with the base-induced rearrangement to give 2-bromohexa-1,2,4-triene [43]. A useful route to alkenylidene carbenes involves the ring-opening of 1,1-dibromocyclopropanes under basic liquid:liquid or solid:liquid conditions. The reaction has fairly general applicability and has been applied to the formation of, for example, dimethyl-, phenylmethyl- and diphenylvinylidene carbenes, and their subsequent reaction with a range of electron-rich alkenes [44].

Isopropylidene carbene (Me₂C=C:) is generated efficiently from the enol triflate derived from *iso*-propyl trimethylsilyl ketone using KF/Aliquat [45], but full experimental details are not given. The carbene can be trapped by isocyanides to produce, after solvolysis, *N*-substituted 3-methylbut-2-enoamides in 35–52% yield [46].

Cyclohexylidene carbene and cyclopentylidene carbene have been generated by the base-induced decomposition of the appropriate 1-(*N*-acetyl-*N*-nitrosoaminomethyl)cycloalkan-1-ol in the presence of Aliquat [47–49] and they have been shown to react in high yield with electron rich alkenes (see Section 7.3). Cyclopropylmethylidene, di(cyclopropyl)methylidene, and isopropylidene carbenes have been generated by an analogous route [49].

7.1.18 Generation and reaction of dimethylvinylidene carbene and related compounds

Method A: The reactive substrate (30 mmol) and TEBA-Cl (150 mg, 0.06 mmol) in a two-phase mixture of PhH (4 ml) and aqueous KOH (51%, 50 ml) are stirred for 30 min at 25 °C under N₂. Me₂C(Cl)C≡CH (1.03 g, 10 mmol) in PhH (25 ml) is added slowly over 2.5 h. The mixture is stirred for 10–13 h at 20–25 °C before being diluted with H₂O (200 ml). The aqueous mixture is extracted with Et₂O (4 × 30 ml) and the combined extracts are dried (Na₂SO₄) and evaporated to yield the product.

Method B: An excess of the substrate (20 ml, ca. 0.15–0.3 mol) to be reacted with the carbene and Aliquat or TBA-Br (0.06 mmol) in aqueous NaOH (50%, 7 ml) are stirred for 10 min at room temperature under N₂. Me₂C=C=CHBr (3 g, 20 mmol) in PhH (25 ml) is added slowly over 2.5 h. The mixture is stirred for 16–72 h at 0–60 °C before being diluted with H₂O (200 ml). The aqueous mixture is extracted with Et₂O (4 × 30 ml), and the combined extracts are dried (Na₂SO₄) and evaporated to yield the product.

Method C: TBA-HSO₄ (2.04 g, 6 mmol) in aqueous NaOH (50%, 150 ml), or a mixture of TBA-HSO₄ (0.68 g, 2 mmol) and powdered NaOH (8 g), is added to the appropriate 1,1-dibromocyclopropane (3 mmol) and reactive alkene (12 mmol) in PhH (100 ml). The mixture is stirred vigorously for 24 h at room temperature and flash chromatography of the concentrated organic phase yields the alkenylidenecyclopropane.

7.1.19 Generation and reaction of cyclohexylidene and cyclopentylidene carbene

Aqueous NaOH (50%, 5 ml) is added dropwise over 1 h at –10 to –5 °C to the appropriate 1-(*N*-acetyl-*N*-nitrosoaminomethyl)cycloalkan-1-ol, obtained by nitrosation of the 1-(*N*-acetylaminomethyl)cycloalkan-1-ol (8.55 g, 50 mmol) with NOCl [30], and Aliquat (2.3 g, 10 mmol) in the reactive substrate (100 ml). When the theoretical amount of N₂ has been collected, the mixture is warmed to room temperature for 15 min and then diluted with brine (100 ml) and extracted with Et₂O (4 × 30 ml). The ethereal extracts are dried (Na₂SO₄) and fractionally distilled to yield the insertion adduct.

Cycloheptatrienylidene carbene is generated when trimethylsilyltropylium tetrafluoroborate is treated with a stoichiometric excess of tetra-*n*-butylammonium fluoride in dichloromethane [50]. Although the carbene dimerizes readily, it will react with electron-deficient alkenes (see Section 7.3). Tetra-*n*-butylammonium fluoride in a stoichiometric amount promotes the formation of adamantylidenevinylidene from 2-bromo-2-(trimethylsilylethynyl)adamantane [51].

α-Elimination from 3-substituted 1,1-dihaloprop-2-ynes liberate alkynylhalocarbenes, e.g. :C(Cl)C≡CR, which yield 1-halo-1-(alk-1-ynyl)cyclopropanes, when trapped with alkenes [52, 53]. The analogous reaction with the parent dihalopropyne leads to the formation of chlorovinylidenecarbene, ClCH=C:, via the base-catalysed rearrangement of the initially formed propynylcarbene, and when reacted with alkenes, produces chlorovinylidenecyclopropanes (20–45%) with no evidence of the propynylcyclopropanes [54].

7.1.20 Generation and reaction of alkynylchlorocarbenes and chlorvinylidenecarbenes.

The dichloride (10 mmol) is added dropwise over 15 min to the alkene (0.1 mol), powdered KOH (2.2 g), and TEBA-Cl (0.1 g, 0.5 mmol) in CH_2Cl_2 (20 ml)* and the mixture is stirred at 20°C until all of the dichloride has been consumed (ca. 2–4 h), as shown by GLC analysis. The mixture is filtered and the cyclopropane is isolated by fractional distillation (*alternatively, $n\text{-C}_6\text{H}_{14}$ can be used as the solvent and the reaction conducted at 40–45°C for 3–5 h).

As ‘Makosza’s method’ has effectively replaced the ‘classical’ procedures for the generation of dihalocarbenes, subsequent Sections of this Chapter present only representative examples of the reactions of the dihalocarbenes generated under phase-transfer conditions.

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7.2 INSERTION OF DIHALOCARBENES INTO C–H BONDS

With the exception of adamantane and few related compounds [1–5] in which dichlorocarbene reacts at the tertiary C–H centre, the yields for the majority of insertion reactions into hydrocarbons are low and of little synthetic value (Table 7.1). Reaction also occurs in low yield at benzylic C–H sites [1, 6, 7] and, in the case of simple alkanes, the insertion reaction is promoted by alkoxy groups [1, 6–14]. Thus, whereas methylcyclohexane produces only 4% yield of the 1-dichloromethyl-1-methylcyclohexane, the corresponding yield with 1-methoxycyclohexane is 13% [6]. Similarly, the low yielding reaction of 1-methoxyadamantane with dichlorocarbene produces 1-dichloromethyl-3-methoxyadamantane by insertion into the tertiary C–H site and (2,2-dichloroethoxy)adamantane by reaction at the primary C–H site, which is activated by the methoxy group. No reaction occurs at the secondary C–H sites [2].

Although $\text{Fe}(\text{CO})_3$ -complexed butadiene does not react with dibromocarbene, the corresponding penta-1,3-dienes undergo C–H insertion at the sp^3 carbon atom (27–38%) [15]. Metal carbonyl-complexed cyclohexadiene and 1-methoxycarbonyl-1,2-dihydropyridine also react in a similar manner in 31 and 54% yield, respectively.

Reaction of a *cis/trans* mixture of 2,5-dimethylfuran with dichlorocarbene produces a mixture of the mono and disubstituted derivatives, in 40 and 47% overall yields, respectively [8]. This appears to be the only example of a double insertion of the carbene into two CH bonds of a single molecule.

TABLE 7.1

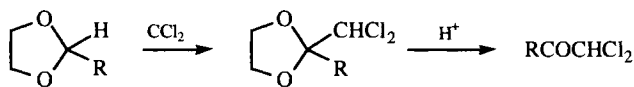
Selected examples of insertion reactions of dihalocarbenes into C-H bonds

Substrate	Carbene	Position of insertion	% yield
Me ₂ CHEt	CCl ₂	2	12
cyclo-C ₆ H ₁₁ Me	CCl ₂	1	5
PhEt	CCl ₂	<i>a</i>	2
	CBr ₂ ^b	<i>a</i>	9
PhCHMe ₂	CCl ₂	<i>a</i>	24
	CBr ₂ ^b	<i>a</i>	16
Tetralin	CCl ₂	1	21
<i>cis</i> -decalin	CCl ₂	9	12–29
	CBr ₂ ^b	9	4
<i>trans</i> -decalin	CCl ₂	9	<3
Adamantane	CCl ₂	1	54
	CBr ₂ ^b	1	35
1-Methyladamantane	CCl ₂	3	~100
1-Methoxyadamantane	CCl ₂	3	trace ^c
1,3-Dimethyladamantane	CCl ₂	5	~100
Diadamantane	CCl ₂	1 and 4 ^d	~100
Trishomobarrelene	CCl ₂	1	64
Trishomobullvalene	CCl ₂	1	59
EtOEt	CCl ₂	<i>a</i>	8
Me ₂ CHOCHMe ₂	CCl ₂	<i>a</i>	43
	CBr ₂ ^b	<i>a</i>	10
cyclo-C ₆ H ₁₁ OMe	CCl ₂	1	13
PhCH ₂ OMe	CCl ₂	<i>a</i>	17
	CBr ₂ ^b	<i>a</i>	13
4-ClC ₆ H ₄ CH ₂ OMe	CCl ₂	<i>a</i>	18
PhCH ₂ OCH ₂ Ph	CCl ₂	<i>a</i>	26
Tetrahydrofuran	CCl ₂	2	18
2,5-Dimethyltetrahydrofuran	CCl ₂	2 and 5 ^e	47
HC(OEt) ₃	CCl ₂	<i>f</i>	14
2-Ethoxy-1,3-dioxolane	CCl ₂	2	56
2-Alkyl-1,3-dioxanes	CCl ₂	2	4–11
	CBr ₂ ^b	2	13–30
2-Aryl-1,3-dioxanes	CCl ₂	2	6–20
2-Alkyl-1,3-dioxolanes	CCl ₂	2	14–70
	CBr ₂ ^b	2	28–34
2-Aryl-1,3-dioxolanes	CCl ₂	2	5–65

^a Insertion occurs at the respective α -position of the alkyl substituent. ^b Using a 3 : 1 ratio of CHBr₃ to substrate. ^c With a trace of 1-(2,2-dichloroethoxy)adamantane. ^d 1- and 4-isomers in a 1.7 : 1 ratio. ^e + 2,5-bis(dichloromethyl) derivatives (40%). ^f Insertion into the tertiary CH.

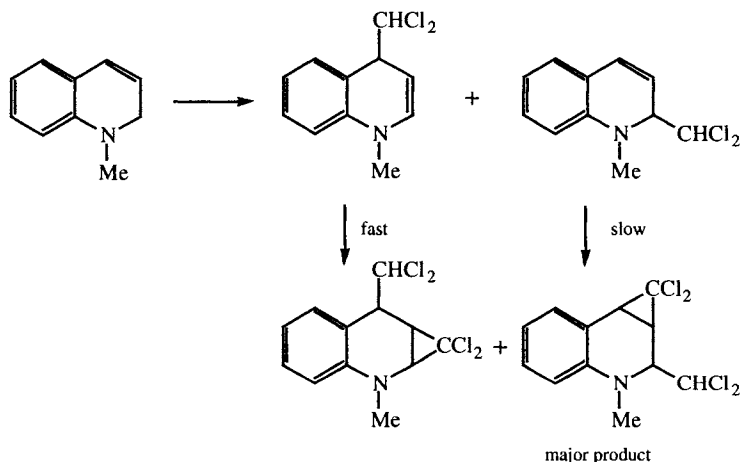
Dioxanes and dioxolanes, derived from alkyl and aryl aldehydes, react with dichlorocarbene specifically at the C-2 position, with no evidence of reaction at C-4 or C-5 (Scheme 7.2). The yields are variable, but provide a convenient route to dichloromethyl ketones [13, 14]. The rate of insertion into the C-H bond correlates with the electronic character of the 2-aryl substituent and is also influenced by

electronic and steric effects of the 2-alkyl substituents [12]. Generally, the rate is reduced by electron-withdrawing substituents and no reaction is observed with the 2-trichloromethyl or 2-(4-nitrophenyl) derivatives [5]. The reaction is shown to be stereospecific with no inversion or racemization at the reactive centre [13,14]



Scheme 7.2

The C–H insertion reaction is aided by amino groups. The ‘allylic’ amino function of 1,2-dihydro-1 methylquinoline promotes the formation of both the 2- and the 4-dichloromethyl derivatives (Scheme 7.3). Spectroscopic monitoring of the reaction shows that the C–H insertion reaction precedes the cycloaddition reaction [16].



Scheme 7.3

7.2.1 Insertion of dichlorocarbene in a C–H bond of a hydrocarbon

The hydrocarbon (6.9 mmol) and TEBA-Cl (23 mg, 0.1 mmol) in PhH (1.0 ml) and aqueous NaOH (50%, 14 ml) are stirred at 40–50°C for 10 min. CHCl_3 (9.0 g, 75 mmol) is added dropwise and the mixture is stirred for a further 6 h. The emulsion is centrifuged and the organic phase is separated. The aqueous phase is extracted with Et_2O (5×25 ml) and the combined organic solutions are dried (Na_2SO_4) and evaporated under reduced pressure to yield the dichloromethyl derivatives.

7.2.2 Synthesis of 2-dichloromethyldioxanes and 2-dichloromethyldioxolanes

Aqueous NaOH (50%, 500 ml) is added to the dioxane (or dioxolane) (0.5 mmol) and TEBA-Cl (1.0 g, 4.4 mmol) in CHCl_3 (500 ml) at 0°C and the two-phase system is stirred

at 800–1000 r.p.m. for 24 h. Na_2SO_4 (300 g) is added with stirring. The mixture is filtered and extracted with Et_2O (3×200 ml), and the dried (Na_2SO_4) extracts are fractionally distilled to yield the 2-dichloromethyl derivative.

7.2.3 Reaction of 1,2-dihydro-1-methylquinoline with dichlorocarbene

Aqueous NaOH (50%, 100 ml) is added to the dihydroquinoline (6 mol) and TEBA-Cl (1.0 g, 4.4 mmol) in CHCl_3 (100 ml) at 0°C . The mixture is stirred for 6 h at 0°C and then overnight at room temperature. Work up, as described in 7.2.1, gives the CH insertion products and dichlorocyclopropyl derivatives.

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7.3 INSERTION OF CARBENES INTO C=C BONDS

The literature which reports examples of the phase-transfer catalysed insertion of dihalocarbenes into C=C bonds is extremely voluminous [see, e.g. (CCl_2) 1–103; (CBr_2) 4, 13, 26, 29, 40, 47, 48, 51, 53, 55, 60, 67, 69, 71, 77, 84, 85, 89, 93, 104–132; (Cl_2) 133; (CFCl) 134–138; (CBrF) 60, 134, 140; (CFI) 141; (CBrCl) 142; (CClI) 133; (CBrI) 143; (CF_2) 144] and no attempt will be made to record every citation.

Phenylthiocarbene, chloro(phenylthio)carbene, their seleno analogues, and the less electrophilic chloro(methylthio)carbene react with a range of alkenes [145–148], as does chloro(phenoxy)carbene [149].

Alkylidene carbenes (isopropylidene [150]; cyclohexylidene [150–152]; cyclopentylidene [150]; cyclopropylethylidene and dicyclopropylmethylidene carbenes [153] and alkenylalkylidene carbenes ($\text{Me}_2\text{C}=\text{C}=\text{C}$: [154–159]; adamantylvinylidene carbene [160]; $\text{MeCH}=\text{CH}.\text{CH}=\text{C}$: [161] react in good yield

with electron-rich alkylethenes and with vinyl ethers under phase-transfer catalytic conditions. Cycloheptatrienyl carbene reacts with electron-deficient alkenes [162].

For convenience, the reactions are reviewed according to substrate type.

Simple alkenes, alkynes and polyenes (Tables 7.2 and 7.3)

The more electronegative the halogens, the less electrophilic and more selective are the dihalocarbenes in their reactions with alkenes. The electronic character of the alkene [163] and steric factors are also influential in determining the ease of insertion of the carbenes into the C=C bond. For example, electron-rich polyalkyl ethenes react extremely readily with all carbenes, whereas 1-chloroethenes have a reactivity approximately half that of the non-halogenated compounds, but are *ca.* five times more reactive than the corresponding 1-bromoethenes [164]. Polyarylethenes react slowly with dichlorocarbene [e.g. 4, 81] and tetraphenylethene is totally unreactive [4]. It is noteworthy, however, that many of the polyarylethenes do not react with dichlorocarbene generated by classical methods. Steric factors also control the stereochemistry and ease of addition of carbenes to hindered C=C bonds [e.g. 27, 54, 59, 79], although it is intriguing that :CClF inserts selectively into the C=C bond of styrene such that the aromatic ring and the fluorine have a *cis* configuration, whereas the corresponding insertion of :CBrF is non-selective [138].

The selectivity and reactivity of the dihalocarbenes is independent of the catalysts used in their generation [165].

1,1-Di-iodocyclopropanes are unstable and cannot be isolated readily [133]. Other dihalocyclopropanes rearrange thermally during work up, or in the presence of the base, to produce ring-opened allylic dihalides or vinyl halides [e.g. 15, 81, 87, 96, 100, 103, 152, 157] (Scheme 7.4). Thermal rearrangement of the dihalocarbene adducts from halocycloalkenes leads to ring expanded products or methylene derivatives [e.g. 87], whereas 1,1-dichlorocyclopent-3-enes produce halobenzenes in high yield [96].

Carbene insertion reactions have been reported with a range of terpenoid compounds [e.g. 9, 10, 40, 57, 66, 86, 91, 93, 115, 126]. In the majority of examples, insertion occurs preferentially on the most highly substituted and electron rich C=C bond. Non-conjugated diene systems frequently react at both sites, e.g. only the bis-insertion adduct in *ca.* 70% yield has been reported for the reaction of limonene with dichlorocarbene [57] but, in contrast, linalool reacts with only one equivalent of dichlorocarbene yielding a product (Scheme 7.5), which results from initial carbene insertion into the non-allylic C=C bond and subsequent ring opening [91]. The reaction of carvone with dichloro- or dibromocarbene depends on the reaction conditions. Insertion of one equivalent of carbene into the electron-rich non-conjugated C=C bond (50–85%), with smaller yields of the bis-insertion adduct (~10%), is observed with an excess of the haloform at 65–70°C [93, 115]. At lower temperatures with two equivalents of carbene, insertion into the α,β -conjugated C=C bond occurs [93, 113, 115]. Reaction of dihalocarbenes with terpenes having 1,1-disubstituted exo-cyclic and 1,2-disubstituted endo-cyclic C=C bonds (e.g. verbenene)

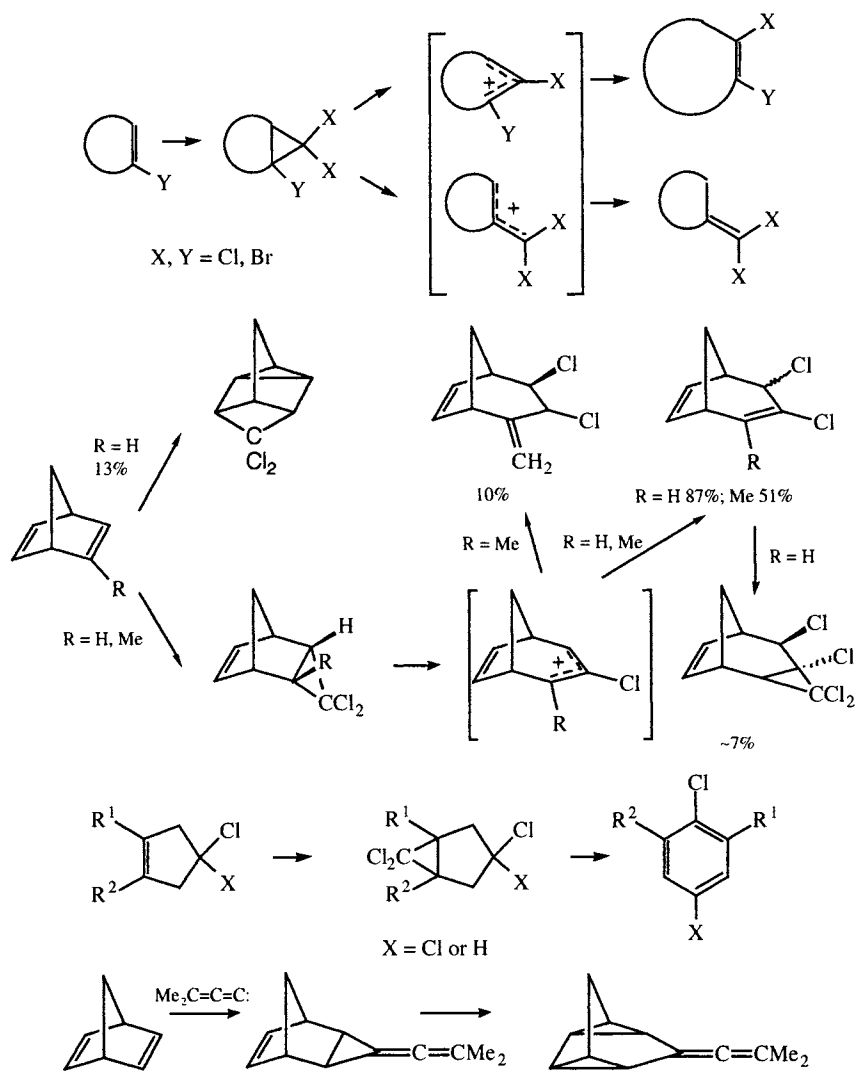
TABLE 7.2

Selected examples of the reaction of carbenes with alkyl and arylalkenes

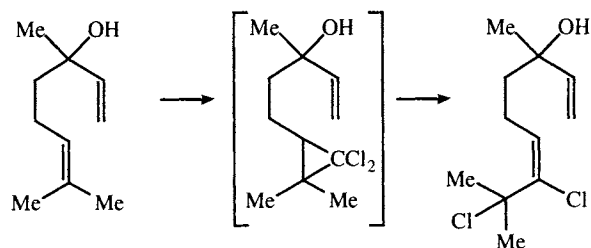
R ¹ R ² C=CR ³ R ⁴				Reaction conditions	% yield
<i>Reaction with CF₂</i>					
R ¹ = Me	R ² = Me	R ³ = Me	R ⁴ = Me	7.1.14/20°C/27 h	70
Me	Me	Me	H	7.1.14/20°C/27 h	60
Ph	Me	H	H	7.1.14/20°C/30 h	30
<i>Reaction with CCl₂</i>					
Me	Me	Me	H	7.1.1/40°C/4 h	60
	-(CH ₂) ₂ -	H	Ph	7.1.1/rt/3 h	55
	-(CH ₂) ₂ -	Ph	Ph	7.1.1/rt/3 h	95
H		-(CH ₂) ₃ -	H	7.1.1/reflux/4 h	82
H		-(CH ₂) ₄ -	H	7.1.1/reflux/4 h	83 ^{a,b}
Ph	H	H	H	7.1.1/40°C/4 h	90 ^c
Me	Me	Me	Ph	7.1.1/40°C/4 h	91
Ph	Me	Me	Ph ^d	7.1.1/40°C/4 h	5
Ph	Me	Me	Ph ^e	7.1.1/40°C/4 h	93
<i>Reaction with CBr₂</i>					
Me	Me	Me	H	7.1.3/40°C/2–3 h	81
H	H	Me	CH ₂ Br	7.1.3/40°C/2–3 h	85 ^f
	-(CH ₂) ₂ -	H	Ph	7.1.3/rt/3 h	50
	-(CH ₂) ₂ -	Ph	Ph	7.1.3/rt/3 h	60
H		-(CH ₂) ₄ -	H	7.1.3/40°C/96 h	72
<i>n</i> -Bu	H	H	SiMe ₃	7.1.3/55°C/21 h	80
H	H	Me	CH ₂ CO ₂ H	7.1.3/60°C	80
H		-(CH ₂) ₄ -	CH ₂ CO ₂ H	7.1.3/60°C	55
Ph	H	H	H	7.1.3/rt/72 h	66
Ph	Me	H	H	7.1.3/40°C/2–3 h	80
Ph	Ph	H	H	7.1.3/40°C/2–3 h	34
Ph	H	H	Me ^e	7.1.3/40°C/2–3 h	23
Ph	H	H	CH ₂ Br ^e	7.1.3/40°C/2–3 h	92 ^f
Ph	H	H	Ph ^e	7.1.3/40°C/2–3 h	32
<i>Reaction with Cl₂</i>					
Ph	H	H	H	7.1.7/50°C/3 h	21
<i>Reaction with CClF</i>					
Me	Me	Me	H	7.1.8/0°C/30 min	43
Me	Me	Me	Me	7.1.8/2–3 d	50
Me	Me	Cl	H	7.1.8/30°C/12 h	46
Ph	Ph	Cl	H	7.1.8/30°C/12 h	53
<i>Reaction with CBrF</i>					
Me	Me	H	H	7.1.9/reflux/3 h	81
Me	Me	Me	Me	7.1.9/2–3 d	45
H		-(CH ₂) ₃ -	H	7.1.9/reflux/4 h	79
H		-(CH ₂) ₄ -	H	7.1.9/reflux/4 h	77
Ph	H	H	H	7.1.9/reflux/3 h	84
Ph	Me	H	H	7.1.9/reflux/3 h	88
<i>Reaction with CClBr</i>					
Me	Me	Me	Me	7.1.13/25°C/21 h	60
Me	Me	Me	H	7.1.13/25°C/21 h	75
H		-(CH ₂) ₆ -	H	7.1.13/45°C/21 h	70
Ph	Me	H	H	7.1.13/45°C/21 h	71

R ¹ R ² C=CR ³ R ⁴				Reaction conditions	% yield
<i>Reaction with ClF</i>					
H	-(CH ₂) ₄	H	H	7.1.10/20°C/4 h	20
Ph	H	H	H	7.1.10/20°C/4 h	60
Ph	H	H	Me	7.1.10/20°C/4 h	17
<i>Reaction with CCl</i>					
Et	Me	H	H	7.1.11/50°C/3 h	65
Ph	H	H	H	7.1.11/50°C/3 h	49
<i>Reaction with CBrI</i>					
Ph	Ph	H	H	7.1.12/rt/17 h	10 ^g
<i>Reaction with MeSCCl</i>					
Me	Me	Me	Me	7.1.17/45°C/3 h	43 ^h
Me	H	H	Me	7.1.17/45°C/3 h	8 ⁱ
<i>Reaction with PhSCH</i>					
H	-(CH ₂) ₄	H	H	7.1.15/45°C/2 h	67
Me	H	H	Me ^f	7.1.15/45°C/2 h	79
Me	H	H	Me ^d	7.1.15/45°C/2 h	65
Ph	H	H	H	7.1.15/45°C/2 h	70
Ph	H	H	Ph ^f	7.1.15/45°C/2 h	78
<i>Reaction with PhSCCl</i>					
H	-(CH ₂) ₄	H	H	7.1.15/45°C/2 h	44
Ph	H	H	H	7.1.15/45°C/2 h	63
<i>Reaction with PhSeCH</i>					
H	-(CH ₂) ₄	H	H	7.1.16/rt/2 h	70 ^k
Me(CH ₂) ₄	H	H	H	7.1.16/rt/2 h	51 ^l
<i>Reaction with PhSeCCl</i>					
H	-(CH ₂) ₄	H	H	7.1.16/rt°C/2 h	49
<i>Reaction with PhOCCl</i>					
4-MeC ₆ H ₄	H	H	H	7.1.1 ^j	11 ^m
<i>Reaction with Me₂C=C=C</i>					
H	-(CH ₂) ₄	H	H	7.1.18.A/rt/3 h	37
Me	Me	Me	Me	7.1.18A/rt/3 h	87
Ph	H	H	H	7.1.18A/rt/3 h	81
Ph	Me	H	H	7.1.18.C/rt/24 h	62
<i>Reaction with PhMeC=C=C</i>					
Me	Me	Me	Me	7.1.18.C/rt/24 h	55
<i>Reaction with Ph₂C=C=C</i>					
Me	Me	Me	Me	7.1.18.C/rt/24 h	70
<i>Reaction with cyclopropylmethylidene carbene</i>					
H	-(CH ₂) ₄	H	H	7.1.19/40°C/5 h	52
<i>Reaction with dicyclopropylmethylidene carbene</i>					
H	-(CH ₂) ₄	H	H	7.1.19/40°C/5 h	64
<i>Reaction with cyclohexylidene carbene</i>					
H	-(CH ₂) ₄	H	H	7.1.19/40°C/5 h	78
H	-CH ₂ CH=CHCH ₂ -	H	H	7.1.19/40°C/5 h	65

^a 77% using 7.1.2 after 15 min. ^b 98% using cetrimide. ^c 80% using 7.1.2 after 15 min. ^d Z-isomer. ^e E-isomer. ^f Using cetrimide. ^g + 6.5% dibromo compound. ^h + 24% MeS(Cl)C=C(Cl)SMe. ⁱ + 72% MeS(Cl)C=C(Cl)SMe. ^j Using PhOCHCl₂ instead of CHCl₃. ^k 15% under liquid:liquid conditions. ^l 18% under liquid:liquid conditions. ^m + PhO(Cl)C=C(Cl)OPh.



Scheme 7.4



Scheme 7.5

TABLE 7.3
Selected examples of the reaction of carbenes with conjugated dienes

<div style="display: flex; justify-content: space-around;"> A B </div> <div style="display: flex; justify-content: space-around;"> $R^1R^2C=CR^3$ $CR^4=CR^5R^6$ </div>						Carbene	Position of attack	% yield of adduct (reaction conditions)
R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶			
H	H	H	H	H	H	:CCl ₂	A and B	12 + 39 (rt/3 h; 1 : 1.5 ^a)
Cyclopentadiene						:CCl ₂	A/B	10 (rt/3 h; 1 : 2.5 ^a)
Ph	H	H	H	H	H	:CCl ₂	B	88 (0°C/12 h; 1 : 1 ^a)
						:CCl ₂	B and A	66 + 10 (0°C/12 h; 1 : 2.5 ^a)
H	H	H	Me	H	H	:C(SPh)Cl	B	51 (40°C/12 h; 1 : 1 ^a)
H	H	H	Me	H	H	Me ₂ C=C=C:	B	26 (25°C/30 min; 1 : 3 ^a)

^a Ratio of diene:carbene precursor.

occurs preferentially on the *exo* bond [22, 126]. Carbene insertion by dimethylvinylidene carbene into α - and β -pinene and carene have been reported in low yields (20–30%) [156].

As noted with the reactions between terpenes and dihalocarbenes, mono-insertion adducts at the more electron-rich sites can be isolated from the reaction of non-conjugated acyclic and cyclic dienes although, depending on the reaction conditions, the bis-adducts may also be formed. Norbornadiene produces both 1,2-*endo* and 1,2-*exo* mono-insertion adducts with dichlorocarbene, as well as a 1,4-addition product (Scheme 7.4) [67]. The mono adduct produced from the reaction with dimethylvinylidene carbene rearranges thermally to yield the ring-expanded product (Scheme 7.4) [157]; a similar ring-expanded product is produced with cyclohexylidene carbene [149].

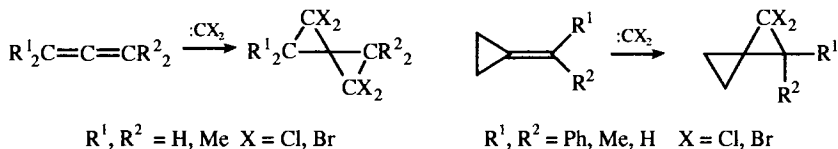
When bis-adducts are formed, both *syn*- and *anti*-isomers (from the cyclic dienes) and meso and racemic mixtures (from the acyclic dienes) are detected [e.g. 4, 57, 127, 142], the ratio depending to a large extent on steric factors within the substrate. 1,2-Divinylbenzene reacts with two equivalents of dibromocarbene to give a mixture of the *d,l* and racemic adducts [106, 124].

Cycloocta-2,5-diene yields the mono adduct with dimethylvinylidene carbene (~19%) [156]. With dichloro- and dibromocarbene, the *syn*- and *anti*-bis-adducts are obtained in a ratio which favours the *syn*-isomer [55, 104] whereas, with bromochlorocarbene, the mono-adduct is reported to be the major product (55%) with only 9% of the bis-adduct [142]. In contrast, cyclo-octatetraene is converted into the mono-, *syn*-1,2:5,6-bis-, tris-, and tetra-adduct with dichlorocarbene depending on the reaction conditions [4, 17, 25, 55] and the 1,2:5,6-bis-adduct with

dibromocarbene [104], whereas *cis,trans,trans*-cyclododeca-1,5,9-triene produces the mono-, bis- and tris-insertion adducts, depending on the reaction conditions and the catalyst used [40, 86]. The mono-adduct predominates (72%), when tetramethylammonium chloride is used; the bis-adduct, when benzyltriethylammonium chloride (81%) or *N*-benzylephedrinium chloride (60%) is used; and the tris-adduct, when cetyltrimethylammonium chloride (81%) is used. Early claims [40] that the carbene is activated by the hydroxyethylammonium catalyst to preferentially attack a *trans* C=C bond has been disproved [86], as has the claim that ephedrinium salts induce asymmetry in the products. The all *trans*-isomer produces only the mono-adduct in 64% yield [95]. *cis,trans*-Deca-1,5-diene produces the two mono-adducts, together with the bis-adduct in its reaction with dibromocarbene [127].

Conjugated dienes yield mono-adducts with dihalocarbenes at the more electron-rich C=C bond; further reaction at the less reactive bond may also occur [e.g. 4, 8, 19, 23, 31, 37, 49, 62, 69, 94]. Cycloheptatriene yields the *syn*- and *anti*-1,2:5,6-bis-adducts (14.5 and 22.9%) and the *syn*-1,2:5,6-*anti*-3,4-tris-adduct with dichlorocarbene [62]. The facile reaction of cyclopropylethenes with dihalocarbenes produces dicyclopropyl compounds [53, 117]. Isoprene reacts with chloro(phenylthio)carbene across the more reactive 1,2-bond (51%) [146].

2-Vinylbuta-1,3-diene produces the 1,2- and 3,4-mono-insertion adducts with dichlorocarbene in a 4 : 1 ratio [37]. A similar preference in reactivity is observed with 3-methylene-cyclohexenes [90]. 1,2-Dienes react with two equivalents of dichlorocarbene to form spiropentanes [21, 90] (Scheme 7.6). Spiropentanes (50–95%) are also obtained from methylenecyclopropanes [36, 106] and by the reaction of electron-deficient alkenes with an excess of chloroform [31] (see Scheme 7.12)



Scheme 7.6

Alkynes tend to be much less reactive than alkenes. For example, 1,2-diphenylethyne produces only 23% of the dichlorocyclopropene from its reaction with dichlorocarbene, compared with 96% of the dichlorocyclopropane obtained from *trans*-stilbene under analogous conditions [4]. Conjugated enynes react preferentially at the C=C bond with dihalocarbenes [18–20, 22, 38] and with dimethylvinylidene carbene [158].

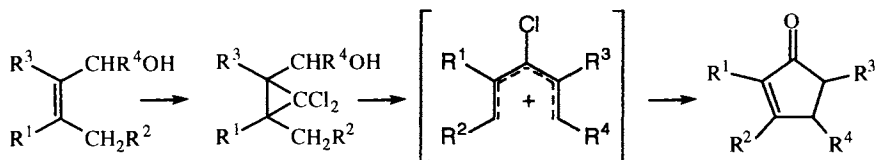
Although the C=C bond of allyl alcohols is frequently less susceptible to reaction with dihalocarbenes, insertion of the carbene into the C=C bond invariably occurs (Table 7.4) to the exclusion of reaction at the hydroxyl group (see Section 7.5) [98]. A complex mixture of products is obtained from the reaction of dichlorocarbene with allyl alcohol, but the cyclopropane can be obtained in high overall yield (>70%) via

TABLE 7.4
Selected examples of the reaction of carbenes with allylic alcohols

R ¹	R ²	R ³	R ⁴	R ⁵	Method	% yield of cyclopropane
<i>Reaction with CCl₂</i>						
H	H	H	Me	H	7.1.1	0 ^a
Me	Me	H	Me	H	7.1.1	92
Me	H	H	H	H	7.1.1	74
Me	<i>n</i> -C ₅ H ₁₁	H	H	H	7.1.1	79
Me	H	H	Me	H ^b	7.1.1	68
Me	H	H	Me	H ^c	7.1.1	75
Me	Me	H	Me	H ^b	7.1.1	77
H	H	Me	Me	H	7.1.1	53
<i>Reaction with ClF</i>						
H	H	H	H	H	7.1.10	15
<i>Reaction with Me₂C=C=C</i>						
Me	H	Me	H	H	7.1.18	16
H	H	Me	H	H	7.1.18	14
Ph	H	H	H	H	7.1.18	21

^a 75% via diallyl acetal. ^b *trans*-isomer. ^c *cis*-isomer.

carbene insertion into the C=C bond of allyl acetals, followed by hydrolysis [56, *cf.* 61]. Allyl alcohol reacts with chlorofluorocarbene in low yield [135, 136]. Under favourable circumstances, acid-catalysed ring opening of initially formed 1,1-dichloro-2-hydroxymethylcyclopropanes leads to cyclopent-2-enones (Scheme 7.7) [35, 74].



Scheme 7.7

Acyclic and cyclic allylic ethers and acetals react normally with dihalocarbenes at the C=C bond [e.g. 77, 85, 108, 114, 121, 122]. Carbene insertion into the C=C bond of allylic ketones, which can be complicated by competitive reaction by the carbonyl group, can also be effected via the initial formation of the acetal and has been used in the synthesis of cyclonona-3,4- and -4,5-dienones from cyclooctenones [125].

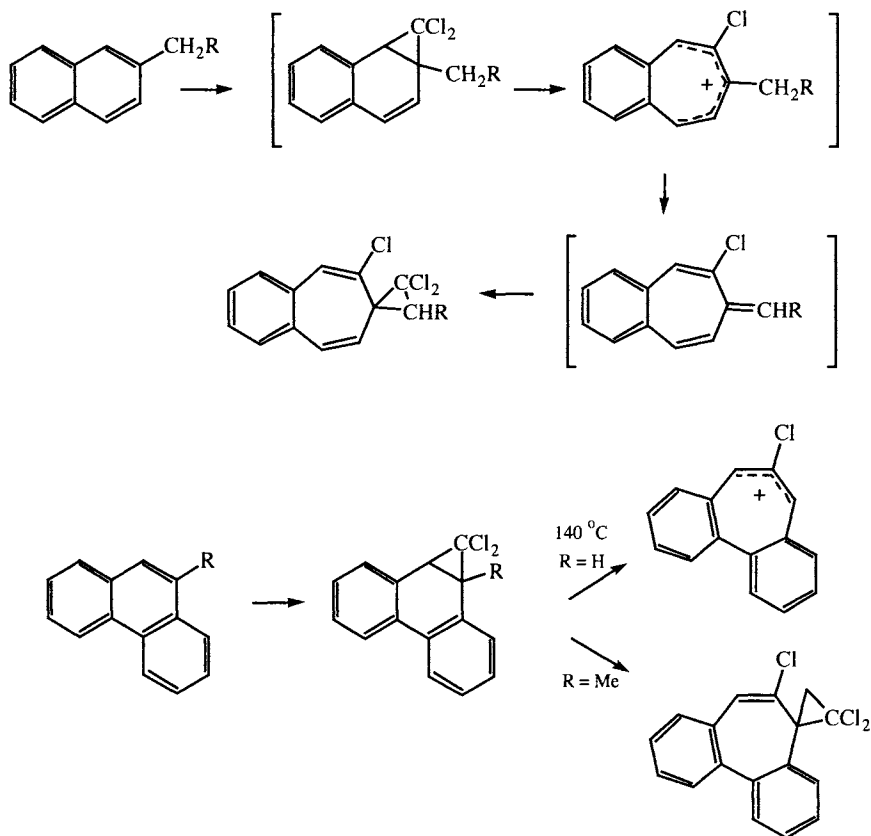
7.3.1 Synthesis of cyclopent-3-enones from allylic alcohols

Aqueous NaOH (50%, 2 ml) is added dropwise to the allylic alcohol (5.6 mmol) and HDTMA-Br (50 mg, 0.14 mmol) in CHCl₃ (1 ml) under N₂ at 55 °C. The mixture is stirred for *ca.* 3 h, neutralized with HCl (10%), and extracted with CH₂Cl₂ (3 × 10 ml).

Evaporation of the dried (MgSO_4) extracts gives the dichlorocyclopropane, which is then heated in aqueous HBr (47%) at 100°C for 9 h. The mixture is diluted with H_2O and extracted with CH_2Cl_2 . Evaporation of the extracts produces the cyclopent-3-enone.

Arenes

Addition of carbenes to π -electron excessive aromatic compounds, or those which possess a high degree of bond fixation, is well established. Dihalocarbenes react with naphthalenes with ring expansion to produce benztrapylum systems (Scheme 7.8). Loss of hydrogen halide from the initially formed product leads to an alkene which reacts with a second equivalent of the carbene to yield the spirocyclopropyl derivatives in high yield (>95%) [14, 50]. Insertion into the alkyl side chain (see Section 7.2) also occurs, but to a lesser extent [14]. Not unexpectedly, dichlorocarbene adds to phenanthrenes across the 9,10-bond [9, 10, 14], but it is remarkable that the three possible isomeric spiro compounds could be isolated (in an overall yield of 0.05%!) from the corresponding reaction with toluene [14].

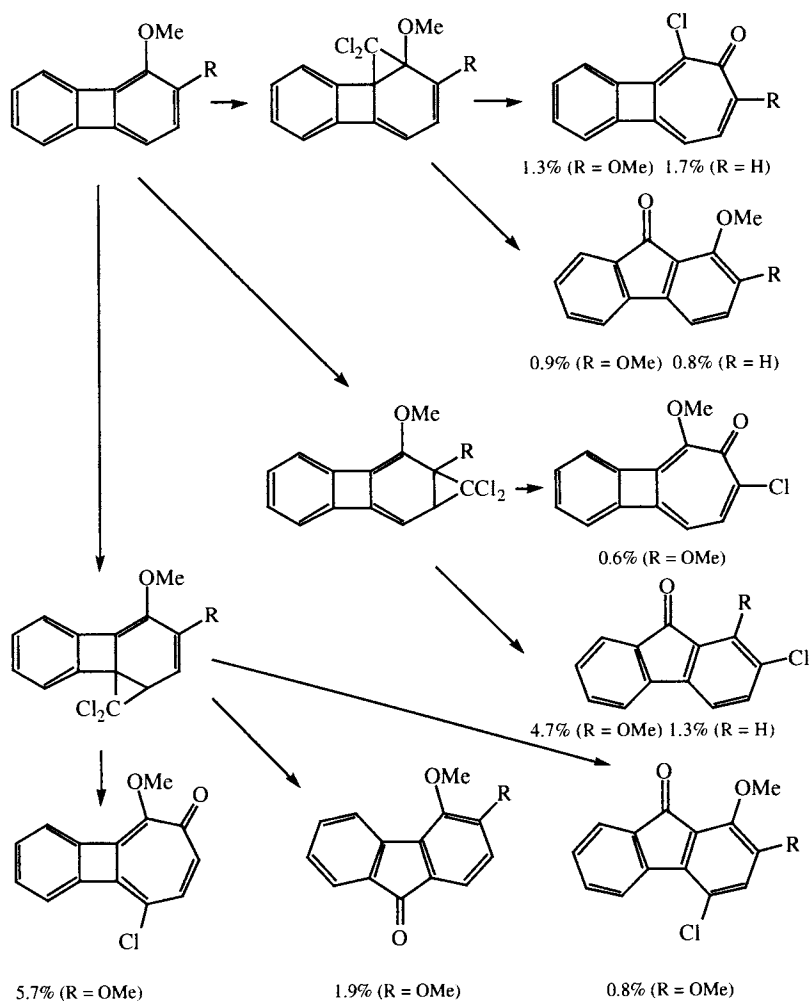


Scheme 7.8

7.3.2 Typical procedure for the reaction of arenes with dichlorocarbene

Aqueous NaOH (50%, 30 ml) is added dropwise over 15 min to the arene (50 mmol) and CTMA-Cl (1.33 g, 5 mmol) in CHCl_3 (12 ml) at 50°C . The mixture is stirred for a further 2.5 h and then diluted with H_2O (100 ml) and acidified to pH 2 with H_2SO_4 (10%). The aqueous mixture is extracted with EtOAc (3×50 ml) and the dried (Na_2SO_4) extracts are evaporated to give the insertion products.

The combination of mesomeric electron-donating effects of the methoxy groups and the high bond fixation of the system results in high reactivity of 1-methoxy- and 1,2-dimethoxybiphenylene [28, 63] with dichlorocarbene to produce a complex mixture of ring-expanded products (Scheme 7.9).

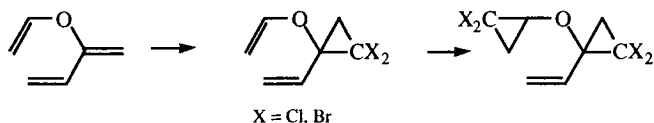


Scheme 7.9

Carbenes react readily with π -excessive heteroaromatic systems to give, in general, ring-expanded products (see Section 7.7).

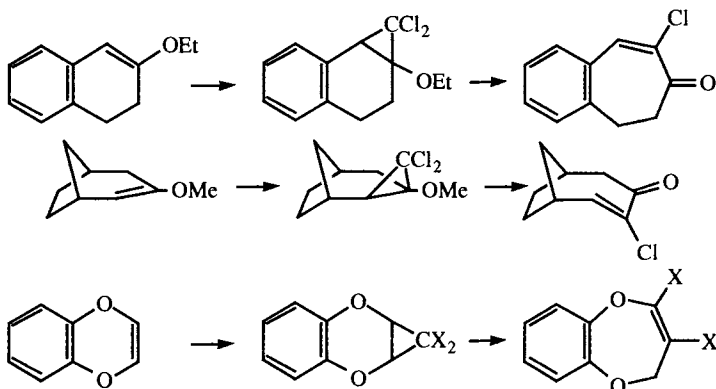
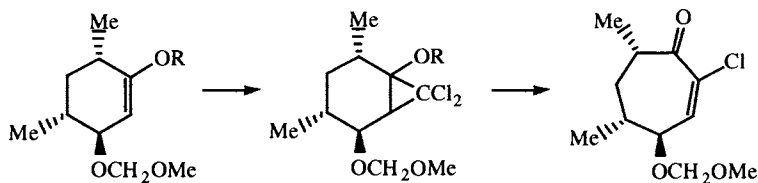
π -Electron-excessive alkenes

As one might expect, the mesomeric effect of an alkoxy group enhances the activity of the C=C to attack by the carbene, but it has been noted that, where there is competition between an alkoxyvinyl group and an 'inactivated' alkene group within the same molecule, an alkyl or aryl group stabilizes the transition state better than does the vinyloxy group (Scheme 7.10) [56]. It is noteworthy that vinyl sulphides are five times more reactive than are the enol ethers [62].



Scheme 7.10

Enol ethers [33, 99, 105, 119, 132, 145, 146, 150, 151, 154, 170], vinyl acetals [44, 45], and enol esters [12, 168, 169, 171], unsaturated sugars [67], vinyl sulphides [76, 145] and enamines [32, 35, 172] react readily with a range of halo- and non-halo-carbenes, using the procedures described in Section 7.1, to produce the corresponding cyclopropane derivatives in good yield (Table 7.5). The reaction of



Scheme 7.11

TABLE 7.5
Selected examples of the reaction of carbenes with π -excessive alkenes

$R^1R^2C=CR^3X$				Carbene	% yield
$R^1 =$	$R^2 =$	$R^3 =$	$X =$		
H	H	Me	MeO	CF_2	45
H	H	H	$MeCO_2$	CCl_2	0 ^a
Me	H	Me	$MeCO_2$	CCl_2	47
Me	Me	Me	$MeCO_2$	CCl_2	74
H	$-(CH_2)_{10}-$		EtO	CCl_2	71
H	$-(CH_2)_{12}-$		EtO	CCl_2	63
H	H	H	EtS	CCl_2	52
H	$-(CH_2)_2S$		H	CCl_2	30
H	H	Me	MeO	$CBrCl$	50
H	H	H	<i>n</i> -BuO	CBr_2	50
H	H	H	EtS	CBr_2	39
H	$-(CH_2)_2S$		H	CBr_2	25
H	H	H	<i>n</i> -BuO	$PhSCCl$	58
H	H	H	<i>n</i> -BuS	$PhSCCl$	49
H	H	H	EtO	$PhSCH$	60
H	H	Ph	MeO	$Me_2C=C$	35
H	H	H	<i>i</i> -PrO	$Me_2C=C=C$	48
H	$-(CH_2)_3O$		H	$Me_2C=C=C$	51
H	H	H	EtO	cyclohexylidene	83
H	H	H	<i>t</i> -BuO	cyclohexylidene	60
H	H	H	PhO	cyclohexylidene	60
H	H	Me	MeO	cyclohexylidene	64
H	H	Et	EtO	cyclohexylidene	63
H	H	H	EtO	cyclohexylidene	80
H	H	Me	MeO	cyclopentylidene	66

^a 1,1,1-trichloro-2-acetoxypropane formed.

1-ethoxycyclododecene provides a simple route to *d,l*-muscone, when the initially formed dichlorocyclopropane is opened with methyl lithium [33]. Other cyclic enol ethers tend to undergo a base, or thermally induced ring expansion following the initial insertion of the carbene into the C=C bond [e.g. 64, 68, 70] (Scheme 7.11). 1-Ethoxy-1-oxiranylethene reacts with dibromocarbene to produce, after ring-opening and dehydrobromination, 3-oxiranyl-3-oxoprop-1-yne [132].

1,4-Dioxenes react, as expected, to produce thermally unstable dihalocyclopropanes in high yield [51, 89]. Upon heating, the bicyclic system rearranges to yield the dichloromethyl-1,4-dioxene, whereas the tricyclic system, derived from the benzo-1,4-dioxene undergoes ring expansion to produce the benzo-1,5-dioxepin (Scheme 7.11).

Vinyl acetate fails to react with dihalocarbenes, but reacts with the trihalomethyl anion precursor to produce the 1,1,1-trihalo-2-acetoxypropane [33, 166–168]. In contrast, where the α -position is substituted by an alkyl group, normal cyclopropanation occurs. Cyclic enol acetates behave in a similar fashion to the enol ethers [12, 88], e.g. bicyclo[3,2,1]oct-2-enyl acetate and its 3-isomer

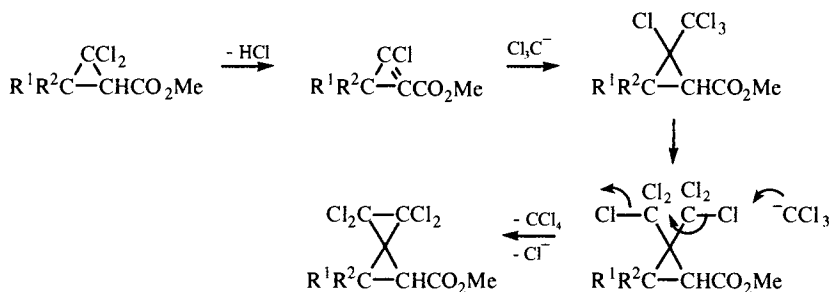
produce 3,3-dichloro-*exo*-tricyclo[4,2,10^{2,4}]nonyl acetates (60–67%) using the phase-transfer catalytic procedure [36], whereas they do not react under ‘classical’ conditions.

1-Phenoxy-2-chloroethene produces the trichloromethyl derivative to the exclusion of the cyclopropane [37]. The reaction of chloroform under basic two-phase conditions with enol esters gives either the expected dichlorocyclopropane or products derived from the addition of the trichloromethyl anion to the alkene. The latter reaction predominates with enols derived from aldehydes and is also dependent on the choice of phase-transfer catalyst. Benzyltriethylammonium chloride clearly controls the course of the reaction in one direction depending on the structure of the enol ester, whereas tetramethylammonium hydrogen sulphate promotes the formation of mixtures of the cycloadducts and the trichloromethyl adducts. The reaction mechanism has been studied [171].

π -Electron-deficient alkenes

Not surprisingly, electron-poor systems react with chloroform, bromoform and other haloalkanes under basic conditions by Michael-type addition of the trihalomethyl anion to the C=C bond. However, a subsequent base-catalysed ring closure to give the cyclopropane derivatives frequently occurs [e.g., 6, 7, 26, 31, 39, 72, 84, 93, 111, 113, 115, 118].

With the exception of the parent compounds, where the Michael adducts are isolated, acrylic esters [see, e.g. 6, 7, 31, 105, 111] and nitriles [6, 7], and vinyl ketones [26, 113, 115] generally yield the cyclopropanes (Table 7.6) under the standard Makosza conditions with chloroform. Mesityl oxide produces a trichlorocyclopropylpropyne in low yield (10%) [7]. When there is no substituent, other than the electron-withdrawing group at the α -position of the alkene, further reaction occurs with the trichloromethyl anion to produce spiro systems (35–48%) (Scheme 7.12) [7, 31]. Under analogous conditions, similar spiro systems are formed with α,β -unsaturated steroidal ketones [39]. Generally, bromoform produces cyclo adducts with all alkenes. Vinyl sulphones are converted into the dichlorocyclopropane derivatives either directly or via the base-catalysed cyclization of intermediate trichloromethyl deriva-



Scheme 7.12

TABLE 7.6

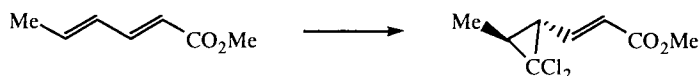
Selected examples of the reaction of haloforms under basic conditions with π -deficient alkenes

$R^1R^2C=CR^3X$				Haloform	% yield of cyclopropane
$R^1 = H$	$R^2 = H$	$R^3 = H$	$X = CO_2Me$	$CHCl_3$	0 ^a
H	H	Me	CO_2Et	$CHCl_3$	85
				$CHBr_3$	78 ^b
H	H	Me	CO_2t-Bu	$CHCl_3$	51
H	H	Ph	CO_2Et	$CHCl_3$	95
				$CHBr_3$	93
Me	H	Me	CO_2Me	$CHCl_3$	69
Ph	H	Me	CO_2Et	$CHCl_3$	0
				$CHBr_3$	6
H	H	H	CN	$CHCl_3$	0 ^c
H	H	Me	CN	$CHCl_3$	42 ^d
H	H	Me	COMe	$CHCl_3$	0 ^e
				$CHBr_3$	85
H	H	<i>n</i> -Pr	COMe	$CHCl_3$	25
				$CHBr_3$	50
H	H	<i>i</i> -Pr	COMe	$CHCl_3$	35
				$CHBr_3$	90
H	H	<i>t</i> -Bu	COMe	$CHCl_3$	35
Me	H	Me	COMe	$CHCl_3$	35 ^f
				$CHBr_3$	70 ^g
Et	H	Me	COMe	$CHCl_3$	50 ^g
				$CHBr_3$	80 ^g
<i>i</i> -Pr	H	Me	COMe	$CHCl_3$	50 ^g
				$CHBr_3$	30 ^g
Me	Me	Me	COMe	$CHCl_3$	50 ^g
				$CHBr_3$	21 ^h
H	$-(CH_2)_4-$		COMe	$CHBr_3$	35
H	H	H	SO_2Et	$CHCl_3$	31
				$CHBr_3$	51
H	$-(CH_2)_2SO_2-$	H		$CHCl_3$	57

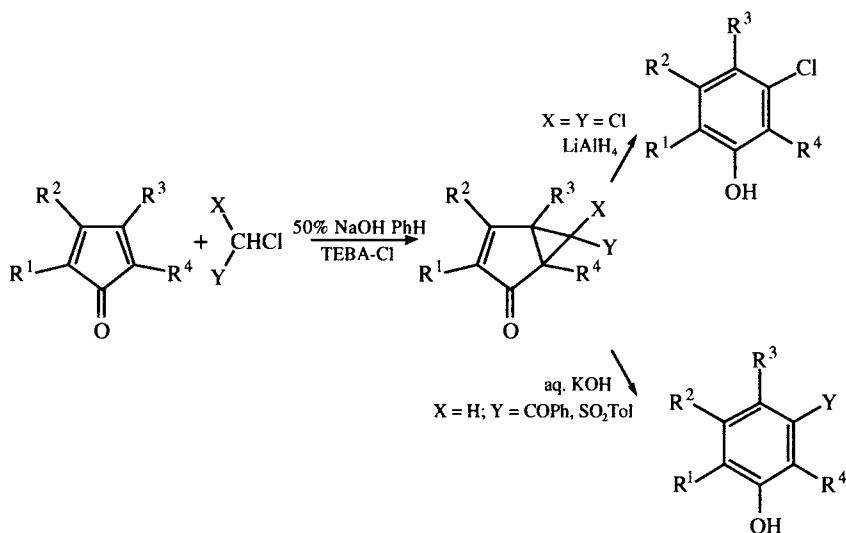
^a 43% Michael adduct. ^b Reaction over 2.5 h at 55–65°C using cetrimide results in hydrolysis of the ester [118]. ^c 72% Michael adduct. ^d + 13% Michael adduct. ^e 50% 4,5-dichloro-3-methylpent-3-en-2-one. ^f Prolonged reaction time.

tives [6, 99]. It has been suggested that the highly selective insertion of dichlorocarbene into the double bond of acrylic esters, when tetramethylammonium catalysts are used, results from the very strong association and consequent low reactivity of the tetramethylammonium trichloromethyl ion-pair [173].

Methyl sorbate reacts with dichlorocarbene in 22% yield at the less electron-deficient γ,δ -unsaturated bond (Scheme 7.13) [31], as does methyl 3-(2,2,6-trimethylcyclohex-1-enyl) propionate (33%).



Scheme 7.13



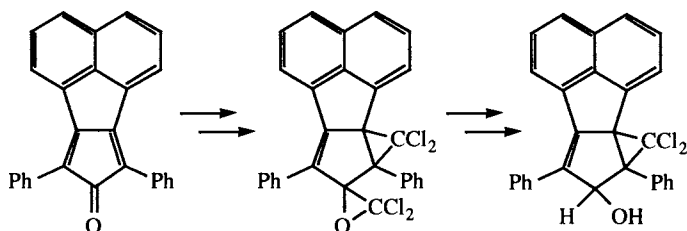
Scheme 7.14

Cyclopentadienones produce 6,6-dihalobicyclo[3,1,0]hex-3-en-2-ones in high yield (>90 % from chloroform, 50–60% from bromoform). Subsequent reduction of the bicyclic products with lithium aluminium hydride produces 3-chlorophenols [84] (Scheme 7.14). In a somewhat analogous manner, phenolic ketones and sulphones have been synthesized via a base-catalysed rearrangement of the initially formed cyclopropane derivatives [174].

7.3.3 Polysubstituted bicyclo[3,1,0]hex-3-en-2-ones

Aqueous NaOH (50%, 50 ml) is added to the cyclopentadienone (1.3 mmol), the haloalkane (0.9 mmol) and TEBA-Cl (0.9 mmol) in PhH (50 ml) and the mixture is stirred at room temperature for *ca.* 12 h. H₂O (100 ml) is then added and the organic phase separated. The aqueous phase is extracted with PhH (2 × 25 ml) and the dried (MgSO₄) extracts are evaporated to yield the cyclopropane derivatives.

The reaction of dichlorocarbene with the fused-ring cyclone (Scheme 7.15) follows an unusual pathway. After initial reaction at the C=C bond, further attack occurs at the carbonyl group. Ring-opening of the oxirane, followed by decarboxylation (see Section 7.4) leads to the final product in 52% yield [73].



Scheme 7.15

The tropone ring of cyclohepta[c]thiophen-6-one reacts preferentially at the C=C bond, instead of at the carbonyl group, with both dichloro- and dibromocarbene to give mono- and bis-adducts in relatively low yields (5–40%) [60]. Benzoquinones produce *anti*-bis-insertion adducts in their reaction with chloroform (95%), or bromoform (57%), under basic conditions [29].

Cyclopropanation reactions of chloroalkanes with π -deficient alkenes under basic phase-transfer catalysed conditions have been observed. Thus, for example, chloroacetic esters and chloroacetonitriles undergo Michael-type reactions with acrylic esters and acrylonitriles, the products of which cyclize to give cyclopropanes (see Section 6.4).

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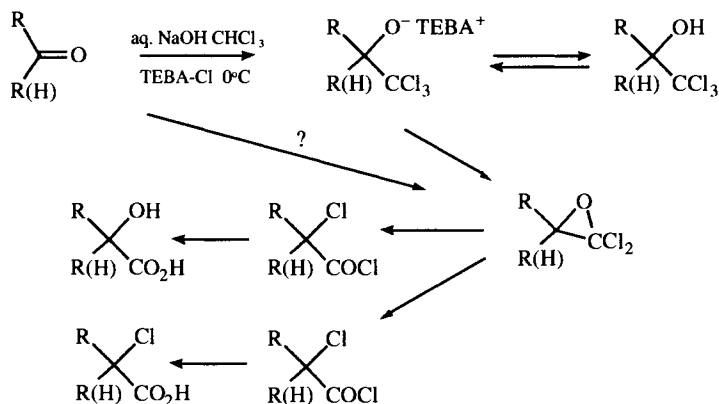
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7.4 REACTIONS OF THE CHLOROFORM/BASE SYSTEM WITH CARBONYL COMPOUNDS

As indicated in Section 7.1, dichlorocarbene is generated via the initial formation of the trichloromethyl anion. Frequently these anions are intercepted by electrophilic species in competition with reactions involving the carbene. Such is the case with the reaction of carbonyl compounds under Makosza's reaction conditions. Aldehydes and ketones yield trichloromethyl carbinols, when they are treated with aqueous sodium hydroxide in the presence of chloroform at 0°C [e.g. 1–3]. Addition of dimethyl sulphate to the reaction mixture results in the formation of the corresponding methyl ethers [3]. At higher temperatures, α -hydroxy and α -chloro carboxylic acids, together with α,β -unsaturated acids, are isolated from the reaction of aliphatic ketones [1–3]. α -Methoxy carboxylic acids have also been obtained from the base-catalysed reaction of ketones with chloroform in the presence of methanol [4]. Generally, when the initially formed trichloromethylcarbinols are reacted with aqueous sodium hydroxide under phase-transfer catalytic conditions, the carbinol either reverts to the aldehyde in the aqueous phase [5], or forms α -chloro acids exclusively [1, 2]. The acids are thought to result from a rearrangement of the initially formed anion (Scheme 7.16) to produce the dichlorooxirane, although direct



Scheme 7.16

insertion of the carbene into the C=O bond, possibly via a $R_2C=O^+-CCl_2^-$ complex, has not been eliminated. The reaction of strained bicyclic ketones under the Makosza reaction conditions yields α -chloroacetyl chlorides, when the products are isolated by distillation but, upon purification of the products by chromatography, dichlorooxiranes are isolated [6]. Where the ketones also have C=C bonds, it is the carbonyl group which reacts preferentially to yield the oxirane.

A combined β -cyclodextrin:quaternary ammonium salt catalyst promotes the addition of the trichloromethyl anion to aromatic aldehydes and enhances the yield of the α -hydroxy acid [7].

7.4.1 Trichloromethylcarbinols

Aqueous NaOH (50%, 64 ml) is added to the aldehyde or ketone (1 mol) and TEBA-Cl (2.3 g, 10 mmol) in $CHCl_3$ (250 ml) at 0°C. The mixture is stirred at 0–5°C for 30–120 min before being poured onto ice (500 g). The mixture is neutralized with concentrated H_2SO_4 and the organic phase is separated, washed well with saturated aqueous $NaHCO_3$ and H_2O , and evaporated to yield the carbinol (Table 7.7).

TABLE 7.7
Selected examples of trichloromethylcarbinols

R^1COR^2		Reaction time	% yield ^a	R^1COR^2		Reaction time	% yield
<i>i</i> -Pr	H	30 min	34 (49)	Me	Me	15 min	69 (81)
Ph	H	1.5 h	80 (91)	Et	Me	15 min	13 (22)
4-MeC ₆ H ₄	H	2 h	– (89)		–(CH ₂) ₄ –	15 min	33 (55)
4-MeOC ₆ H ₄	H	2 h	62 (84)		–(CH ₂) ₅ –	15 min	23 (44)

^a Yields in parentheses refer to the methyl ethers obtained when Me_2SO_4 is added to the reaction mixture.

In temperature-sensitive reactions, aryl aldehydes and ketones produce the trimethylcarbinols at *ca.* 0°C and the glycolic acids at *ca.* 56°C in competition with the base-catalysed Cannizzaro or condensation reactions [3, 5, 8]. 2- and 3-Formylpyridines produce the trichloromethylcarbinols (20–30%), whereas 4-formylpyridine undergoes the Cannizzaro reaction [9]. Formylferrocene is converted into the α -ferrocenylglycolic acid (35%) [10].

When the reaction with substituted benzaldehydes is conducted in the presence of ammonia, the α -amino carboxylic acids are formed [11]. The corresponding reaction involving bromoform is less effective and, for optimum yields, the addition of lithium chloride, which enhances the activity of the carbonyl group, is required. In its absence, the overall yields are halved. The reaction of dichlorocarbene with ketones or aryl aldehydes in the presence of secondary amines produces α -aminoacetamides [12, 13] (see Section 7.6).

7.4.2 α -Hydroxyarylacetic acids

Method A: Aqueous NaOH (50%, 25 ml) is added dropwise over 3–4 h to the aryl aldehyde (0.1 mol) and TEBA-Cl (1.23 g, 5 mmol) in $CHCl_3$ (16 ml) at 56°C. The mixture is

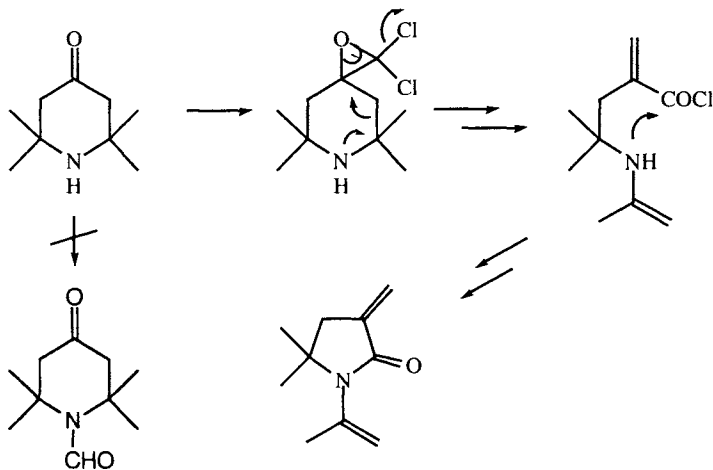
stirred for a further 1 h at 56°C and then cooled and poured into H₂O (100 ml). The mixture is extracted with Et₂O (4 × 25 ml) and the aqueous phase is neutralized with H₂SO₄ (50%). The neutral solution is extracted with Et₂O and the combined extracts are dried (Na₂SO₄) and evaporated to yield the α -hydroxy acid (Ar = Ph, 75%; 4-MeC₆H₄, 80%; 4-MeOC₆H₄, 83%).

Method B: The aromatic aldehyde (50 mmol), CHCl₃ (8.5 g), β -cyclodextrin (1.14 g, 1 mmol) and TEBA-Cl (0.57 g, 2.5 mmol) are stirred at 50°C for 20 min. Aqueous NaOH (50%, 10 ml) is added dropwise and the mixture is stirred for a further 8 h at 50°C. H₂O is added to dissolve any precipitate and the aqueous mixture is washed well with Et₂O. The aqueous phase is adjusted to pH 3 by the addition of aqueous HCl (1 M) and extracted with Et₂O (3 × 30 ml). The dried (Na₂SO₄) extracts are evaporated to yield the α -hydroxy acid (e.g. Ar = Ph, 86%; 4-MeC₆H₄, 83%; 4-MeOC₆H₄, 89%).

7.4.3 α -Aminoarylacetic acids

Gaseous NH₃ is bubbled for 5 min at 0°C through a two-phase system of aqueous NH₃ (33%, 11.2 ml) and CH₂Cl₂ (10 ml) containing KOH (6.72 g, 0.12 mol), LiCl (1.69 g, 0.04 mol) and TEBA-Cl (0.46 g, 2 mmol). The aryl aldehyde (0.02 mol) and CHCl₃ (2.55 ml, 0.03 mol) in CH₂Cl₂ (10 ml) are added dropwise at 0°C over a period of 1 h. The flow of gaseous NH₃ is maintained while the mixture is stirred for a further 6 h at 0°C and then overnight at room temperature. H₂O (30 ml) and CH₂Cl₂ (30 ml) are added and the aqueous phase is separated, washed with CH₂Cl₂ (4 × 20 ml), and concentrated under reduced pressure. The concentrate is adjusted to ca. pH 7 with concentrated HCl and the solution is cooled to 0°C to precipitate the α -aminoarylacetic acid (Ar = Ph, 66%; 4-ClC₆H₄, 81%; 4-FC₆H₄, 50%; 3-FC₆H₄, 59%; 4-MeOC₆H₄, 33%; 4-MeC₆H₄, 29%).

When a carbonyl group and an amino group are present within the same molecule, reaction with dichlorocarbene favours, somewhat unexpectedly, electrophilic attack on the carbonyl group [14, 15]. Although no confirmatory evidence is available, such a reaction pathway (Scheme 7.17) would explain the formation of the ring



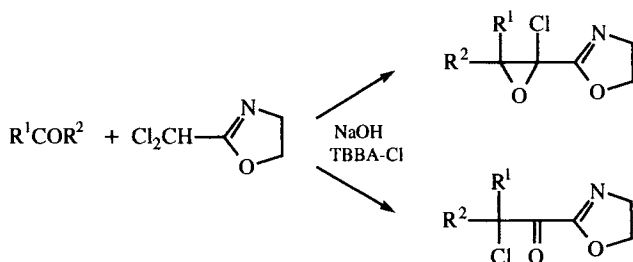
Scheme 7.17

contraction product, to the exclusion of the *N*-formylation of 2,2,6,6-tetramethylpiperidin-4-one (see Section 7.7). In contrast, note that acridone reacts with carbenes preferentially at the nitrogen atom (see Section 7.7).

Conjugated ketones and esters generally react with chloroform under basic conditions by Michael-type addition of the trichloromethyl anion to the C=C bond or by insertion of dichlorocarbene into the C=C bond, depending on the substitution pattern of the conjugated system (see Sections 6.4 and 7.3). The corresponding reaction with bromoform under basic conditions produces 1,1-dibromocyclopropanes.

Acetylarenes are converted into 1,1-dichloro-1-arylcyclopropane-2-carboxylic acids or 2-arylpropionic acids via the initial formation of propenoic acids [16, 17].

In reactions which have some analogy with the interaction of dichlorocarbene/trichloromethyl anions with ketones, 2-dichloromethyloxazolines yield chloro-oxiranes and α -chlorocarbonyl compounds (Scheme 7.18). The formation of the oxiranes is favoured with aldehydes and lower homologue ketones, whereas cyclic ketones and aryl ketones are converted preferentially into the α -chloro carbonyl derivatives [18].



Scheme 7.18

7.4.4 Reaction of 2-dichloromethyloxazoline with carbonyl compounds

2-Dichloromethyloxazoline (5 g, 27.5 mmol) and TBBA-Cl (0.4 g, 1.3 mmol) in CH_2Cl_2 (20 ml) are added to aqueous NaOH (50%, 20 ml). After *ca.* 5 min, the carbonyl compound (30 mmol) is added and the mixture is stirred until the reaction is complete. H_2O (20 ml) and Et_2O (20 ml) are added and the organic phase is separated, washed with aqueous NH_4Cl (sat. soln, 3×10 ml), dried (MgSO_4), and evaporated to yield the product (Table 7.8).

TABLE 7.8

Reaction of 2-dichloromethyloxazoline with carbonyl compounds

R^1COR^2	Reaction conditions	Major product	% yield
$\text{R}^1 = \text{Me}$ $\text{R}^2 = \text{H}$	7.4.4/15 min	Oxirane	60
Et	7.4.4/15 min	Oxirane	75
<i>i</i> -Pr	7.4.4/15 min	Oxirane	95
Me	7.4.4/1 h	Oxirane	95
Ph	7.4.4/30 min	Chloroketone	80
Ph	7.4.4/1.5 h	Chloroketone	83
$-(\text{CH}_2)_5-$	7.4.4/30 min	Chloroketone	95

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7.5 REACTIONS WITH ALCOHOLS, PHENOLS AND EPOXIDES

Alcohols

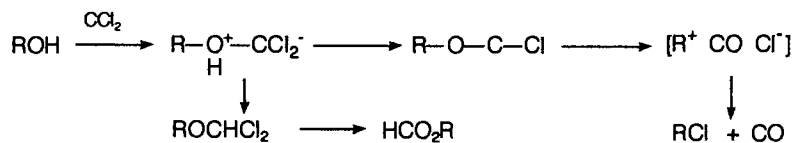
Lower-molecular-weight alcohols react with dichlorocarbene to yield a complex mixture of products, including chloroalkanes. In the case of ethanol, 2,2,2-trifluoroethanol and benzyl alcohol, the major products from the phase-transfer catalysed reaction are trialkyl orthoformates, together with dialkyl carbonates and oxalates [1, 2]. Significant amounts of 1,1,2,3-tetrachloro-2,3-diethoxycyclopropane have also been isolated [3] and it is important to wash commercial chloroform well with water to remove the ethanol stabilizer, in order to prevent the unwanted reactions with the dichlorocarbene. Higher-molecular-weight alcohols react more cleanly with dichlorocarbenes to produce the corresponding chloroalkanes [4], with only negligible amounts of orthoformate esters or elimination products [*cf.* 5]. Steroidal alcohols are converted into the chloro derivatives [6] but, when the hydroxyl group is protected as the ester, insertion of the carbene into a C=C double bond to give a cyclopropane may occur [7]. The mechanism for these reactions has not been established, but it is reasonable to postulate initial electrophilic attack on the oxygen atom, followed by loss of hydrogen chloride. The reactive intermediate can cleave to generate a 'hot' carbenium ion, which reacts without rearrangement to produce the chloroalkane (Table 7.9) having the same stereochemistry as the initial alcohol [6]

TABLE 7.9
Selected examples of the conversion of alcohols into chloroalkanes

Alcohol	Chloroalkane	% yield
Benzyl alcohol	Benzyl chloride ^a	90
1-Hydroxyadamantane	1-Chloroadamantane ^a	94
2- <i>exo</i> -Norborneol	2- <i>exo</i> -Chloronorbornane	90
2- <i>endo</i> -Norborneol	2- <i>endo</i> -Chloronorbornane	44
	2- <i>exo</i> -Chloronorbornane	47
1-Hydroxymethyladamantane	1-Chloromethyladamantane ^b	40
	2-Chlorohomoadamantane	13

^a With traces of the formate ester. ^b + formate ester (35%).

(Scheme 7.19). Prototropic shift of the initial adduct to produce ROCHCl_2 and, subsequently, the formate ester is a less favourable pathway. Alternatively, the carbon monoxide-separated ion-pair can lose a proton leading to an alkene, or cycloadducts derived from further reaction with the carbene. The formation of rearranged products from the reaction of 1-hydroxymethyladamantane suggests that a relatively unencumbered carbenium cation can also be generated, which leads to a Nametkin rearrangement of the system [4].



Scheme 7.19

The reaction of 2- and 4-hydroxyadamantane-1-carboxylic esters with dibromocarbene produces the corresponding 2- and 4-bromo derivatives (10–20%). Slow hydrolysis of the ester groups may also occur under the basic conditions. 1-Acetyl-4-hydroxyadamantane yields 4-bromoadamantane-1-carboxylic acid (37%), as a result of a concomitant reaction with dibromocarbene and a haloform-type reaction [8].

Although allyl alcohol yields a complex mixture of products [9], substituted allylic alcohols react with dihalocarbenes to form, almost exclusively, the hydroxymethylcyclopropanes [10–13], which undergo acid-catalysed ring opening to produce cyclopentenones [9] (see Section 7.3).

7.5.1 Preparation of triethyl and tris(2,2,2-trifluoroethyl) orthoformates

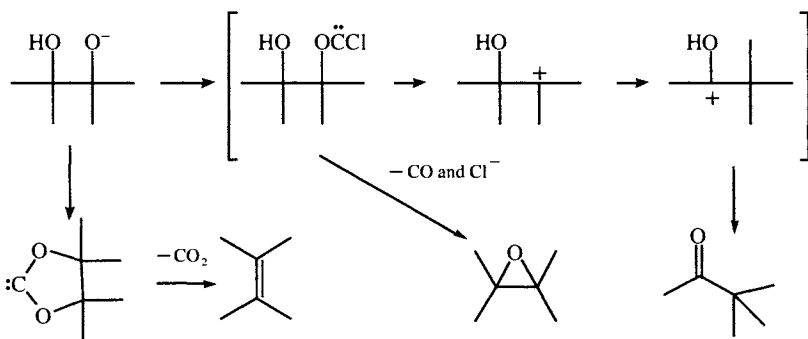
The alcohol (0.5 mol) is added dropwise with stirring at $<20^\circ\text{C}$ over *ca.* 40 min to TEBA-Cl (1.1 g, 5 mmol) in aqueous NaOH (50%, 80 ml) and CHCl_3 (198 g, 1.65 mol). The mixture is stirred at room temperature for 1 h and then poured into ice–water (100 g). The organic phase is separated and the aqueous phase extracted with CHCl_3 (2×25 ml). The combined CHCl_3 solutions are washed with ice-cold H_2O until neutral, dried (MgSO_4), and fractionally distilled to yield the orthoformate esters.

7.5.2 Conversion of alcohols into haloalkanes

Method A: The alcohol (0.01 mmol) and TEBA-Cl (0.04 g, 0.18 mmol) in aqueous NaOH (50%, 20 ml) are stirred at 40°C for 15 min and CHCl_3 (16 ml, 0.2 mol) is then added dropwise over a period of 2 h. The exothermic reaction is stirred for a further 2 h and then poured into ice-water (100 ml) and the products are isolated using the procedure described in 7.5.1.

Method B: CHBr_3 (25 ml, ca. 35 mmol) is added with stirring at room temperature over 2 h to the alcohol (12 mmol) and TEBA-Cl (0.4 g, 1.8 mmol) in a PhH (7 ml):aqueous NaOH (50%, 60 ml) two-phase system. The mixture is stirred for a further 2 h, H_2O (30 ml) is then added and the mixture is extracted with Et_2O (5×75 ml). The extracts are washed with H_2O (25 ml), dried (MgSO_4), and evaporated to give the bromoalkane, which is purified by chromatography on silica.

1,2-Diols generally react with dichlorocarbene to produce a mixture of alkenes and chlorinated cyclopropanes or chloroalkanes, depending on the reaction conditions whereas, under phase-transfer catalysed conditions, the major products are the alkenes and epoxides produced by ring closure of the initial adduct (Scheme 7.20) [14]. When an excess of chloroform is used, further reaction of the alkenes with dichlorocarbene produces the cycloadducts. In addition to the formation of the alkene and epoxide, 1,2-dihydroxycyclooctane yields cyclooctanone, via a 1,2-hydride shift within the intermediate carbenium ion.



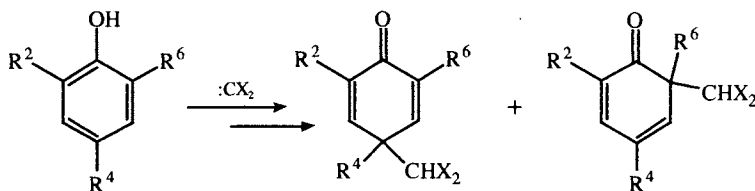
Scheme 7.20

7.5.3 Reaction of 1,2-diols with dichlorocarbene

The diol (20 mmol) and CHCl_3 (7.5 g, 0.63 mmol) in CH_2Cl_2 (100 ml) is added with stirring to aqueous NaOH (50%, 100 ml) and TEBA-Cl (2.0 g, 8.8 mmol). The exothermic reaction is stirred for 2 h and a second volume of CHCl_3 (7.5 g, 0.63 mmol) is added to convert the alkene into the cycloadduct. The mixture is stirred overnight and then poured into H_2O (100 ml). The organic phase is separated and the aqueous phase is extracted with CH_2Cl_2 (2×25 ml). The dried (MgSO_4) organic solutions are evaporated to yield the products, which are purified by chromatography from alumina.

Phenols

Because of the differential partitioning of hydroxide and phenoxide anions into organic solvents by quaternary ammonium cations, the catalysts generally have little effect on the Reimer–Tiemann reaction of phenols with dihalocarbenes [15]. Cetyltrimethylammonium bromide has been used in the two-phase dichloromethylation of polysubstituted phenols (Scheme 7.21, Table 7.10) under Makosza's conditions [16,17]; ring expansion of the reaction products provides an effective route to tropones. The rate of the reaction is enhanced by ultrasonic radiation [16].



Scheme 7.21

TABLE 7.10

Selected examples of the dichloromethylation of 2,4,6-trisubstituted phenols

R ²	R ⁴	R ⁶	Carbene	% yield	
				2-Substitution	4-Substitution
Me	Me	Me	CCl ₂	23	60 ^a
<i>t</i> -Bu	Me	<i>t</i> -Bu	CCl ₂	0	79
OPr	Me	<i>t</i> -Bu	CCl ₂	37	0
<i>b</i>	Me	<i>b</i>	CCl ₂	76	0

^a The corresponding reaction with :CBr₂ gives 24% 2-substitution and 28% 4-substitution. ^b -(CH₂)₉.

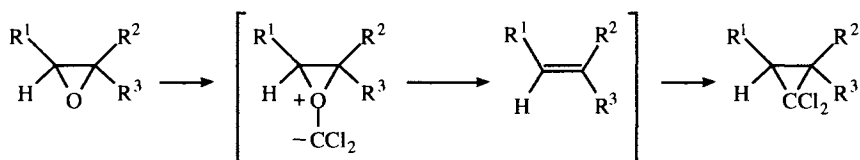
7.5.4 Catalysed Reimer–Tiemann reaction

Aqueous NaOH (10 M, 7 ml) is added over a period of 10 min to the haloform (33 mmol), the phenol (10 mmol) and CTMA-Br (36 mg, 0.1 mmol) at 50 °C. The mixture is stirred for 4 h (30 min with sonication) at 50 °C and then worked up as described in 7.1.1.

There is one reported example of phenols being converted by dichlorocarbene into chlorobenzenes, but the reaction does not appear to be general [6].

Oxiranes

Dichlorocarbene reacts with oxiranes to produce dichlorocyclopropanes [18] via an initial deoxygenation reaction (Scheme 7.22).



Scheme 7.22

7.5.5 Reaction of oxiranes with dichlorocarbene

The oxirane (0.02 mol) in PhH (4 ml) is stirred at 40°C with TEBA-Cl (80 mg, 0.34 mmol) in aqueous NaOH (50%, 40 ml). CHCl_3 (16 ml) is added dropwise over 1 h and the mixture is stirred for a further 3 h. The mixture is diluted with H_2O (50 ml) and extracted with Et_2O (3×30 ml). Evaporation of the dried (Na_2SO_4) extracts yields the dichlorocyclopropane (Table 7.11).

TABLE 7.11
Conversion of oxiranes into dichlorocyclopropanes

			% yield of cyclopropane ^a
$\text{R}^1 = n\text{-C}_8\text{H}_{17}$	$\text{R}^2 = \text{H}$	$\text{R}^3 = \text{H}$	18
$n\text{-C}_{10}\text{H}_{21}$	H	H	15
$-(\text{CH}_2)_4$	H	H	39
Ph	H	H	32 ^b
Ph	H	Me	33
H	Ph	Me	20

^a Based in epoxide consumed. ^b + 2% styrene.

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7.6 REACTIONS OF DIHALOCARBENES WITH AMINES, IMINES, AMIDES AND RELATED COMPOUNDS

Primary amines

Although the extraction of primary amines from a basic medium with chloroform is an inadvisable procedure, on account of the formation of trace amounts of the pungent isonitriles, the specific synthesis of isonitriles by the two-phase reaction of primary amines with chloroform is unreliable. However, the application of the phase-transfer technique [e.g. 1–5] for the controlled release of dichlorocarbene facilitates the synthesis of isonitriles in relatively high yields (Table 7.12).

TABLE 7.12
Selected examples of the synthesis of isonitriles from primary amines

R	Method	% yield	R	Method	% yield
Me	7.6.1.A	50	cyclo-C ₆ H ₁₁	7.6.1.A	48
	7.6.1.B	24	1-Adamantyl	7.6.1.C	54
Et	7.6.1.B	47	2-Adamantyl	7.6.1.C	76
<i>n</i> -Bu	7.6.1.A	60	PhCH ₂	7.6.1.A	40
<i>tert</i> -Bu	7.6.1.A	50	Ph	7.6.1.A	57
<i>n</i> -C ₁₂ H ₂₅	7.6.1.A	41	1-Naphthyl	7.6.1.A	20

7.6.1 Synthesis of isonitriles

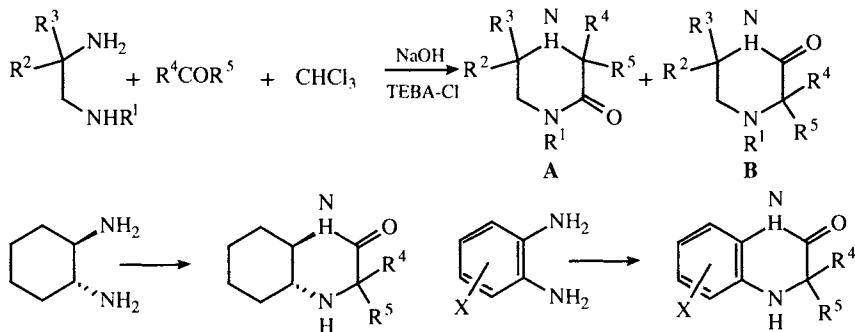
Method A: CHCl₃ (24 g, 0.2 mol) is added with stirring to the amine (0.2 mol) and TEBA-Cl (0.5 g, 2.2 mol) in a two-phase system of CH₂Cl₂ (50 ml) and aqueous NaOH or KOH (50%, 60 ml). The exothermic reaction begins to reflux after *ca.* 10 min and is stirred until the temperature subsides (*ca.* 1 h). H₂O (200 ml) is then added and the organic phase is separated, washed well with dilute HCl, H₂O and brine, dried (K₂CO₃), and fractionally distilled.

Method B: An aqueous solution of the amine (equivalent to *ca.* 0.3 mol of the amine) is stirred with NaOH (35 g, 0.88 mol) and TEBA-Cl (0.6 g, 2.6 mol) in a two phase system of H₂O (12 ml):CHBr₃ (50.3 g, 0.2 mol) in a flask fitted with a cold finger (dry ice-acetone). The mixture is stirred for *ca.* 15 h at 20°C and the organic phase is then separated and worked up as described in 7.6.1.A.

Method C: CHCl₃ (0.179 g, 1.5 mmol) in PhH (3 ml) is added dropwise with stirring at 0°C over 15 min to the amine (1.0 mmol) and TEBA-Cl (20 mg, 0.09 mmol) in PhH (8 ml) and aqueous KOH (50%, 9 ml), and then stirred at 20°C for 4 h. H₂O (10 ml) is added and the aqueous layer is separated and extracted with PhH (20 ml). The combined PhH solutions are washed with H₂O (3 × 10 ml), dried (Na₂SO₄), and evaporated to give the isonitrile.

1,2-Diamines react with dichlorocarbene, generated in the presence of ketones, to produce piperazinones [6, 7]. The carbene probably reacts initially with the ketone to

produce a dichlorooxirane (see Section 7.4), which then reacts with the diamine (Scheme 7.23). Where regioisomers are possible, the reaction is influenced by steric effects. The same products are obtained when 1,1,1-trichloro-2-methylpropan-2-ol reacts directly with the diamine. Further evidence for steric control in the reaction comes from the observation that *trans*-1,2-diaminocyclohexane reacts with the dichlorooxirane, whereas the *cis*-isomer does not [7].



Scheme 7.23

7.6.2 Piperazinones (Table 7.13)

Method A: Aqueous NaOH (50%, 80 ml) is added to a cooled mixture of the 1,2-diamine (0.1 mol), CHCl_3 (16 ml, *ca.* 0.2 mol), the ketone (0.25 mol) and TEBA-Cl (1.14 g, 5 mmol) in CH_2Cl_2 (50 ml). The mixture is stirred overnight at $<10^\circ\text{C}$. H_2O (100 ml) is added and the aqueous phase is separated and extracted with CH_2Cl_2 (2×50 ml). The combined organic solutions are dried (MgSO_4) and evaporated to yield the piperazinone.

TABLE 7.13

Selected examples of the formation of piperazinones

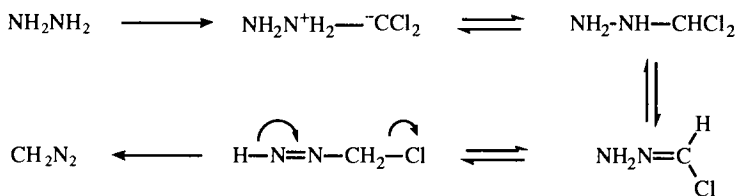
Diamine			ketone		A:B ratio ^{a,b}
R ¹	R ²	R ³	R ⁴	R ⁵	
<i>n</i> -Pr	Me	Me	Me	Me	73 : 27 (85 : 15)
<i>i</i> -Pr	Me	Me	Me	Me	73 : 27 (82 : 18)
<i>i</i> -Pr	Me	Me		$-(\text{CH}_2)_5-$	85 : 15
Ph	Me	Me	Me	Me	87 : 12 (90 : 10)
<i>From trans</i> -1,2-diaminocyclohexane					overall yields
			Me	<i>n</i> -C ₆ H ₁₃	16%
				$-(\text{CH}_2)_4-$	54%
<i>From 1,2-diaminobenzenes</i>					
X = H			Me	Me	82%
				$-(\text{CH}_2)_5-$	74%
				$-(\text{CH}_2)_4-$	72%
X = 4-Me			Me	Me	82% ^c
X = 4-Cl			Me	Me	67% ^c

^a Overall yields 50–60%. A:B ratio refers to Scheme 7.23. ^b Ratios given in parentheses refer to reaction with $\text{CCl}_3\text{CMe}_2\text{OH}$. ^c Mixture of 6- and 7-substituted compounds.

Method B: Aqueous NaOH (50%, 50 ml) is added dropwise at $<10^{\circ}\text{C}$ to the 1,2-diamine (50 mmol), 1,1,1-trichloro-2-methylpropan-2-ol hydrate (17.8 g, 0.1 mol) and TEBA-Cl (0.57 g, 2.5 mmol) in CH_2Cl_2 (100 ml). The mixture is stirred overnight at 10°C and then worked up as described in 7.6.2.A.

Hydrazines

Staudinger and Küpfer's procedure [8] for the generation of diazomethane (Scheme 7.24) has been modified for phase-transfer catalytic conditions [9]. Using tetra-*n*-butylammonium bromide, a yield of 35% of diazomethane, based on the hydrazine consumed, is obtained (a slightly higher yield can be obtained when 18-crown-6 is used [9]).



Scheme 7.24

7.6.3 Preparation of diazomethane

Using apparatus, which is specifically designed for the generation of CH_2N_2 [10], KOH (80 g, 1.4 mol), TBA-Br (0.26 g, 0.8 mmol), H_2O (20 ml), CHCl_3 (32 ml, 0.4 mol) and CH_2Cl_2 (or Et_2O) (200 ml) are mixed in the reaction flask at room temperature. Aqueous NH_2NH_2 (85%, 11.76 g, 0.2 mol) is added and the two-phase system is stirred and heated. After *ca.* 15 min, the characteristic yellow colour of CH_2N_2 appears and co-distils with the volatile solvent. When *ca.* 100 ml of distillate has been collected, CH_2Cl_2 (or Et_2O) is added at a rate equivalent to the distillation rate until the distillate is no longer yellow. The distillate contains *ca.* 3.0 g (0.07 mol) of CH_2N_2 , contaminated with traces of NH_2NH_2 which can be removed by washing the distillate with H_2O (2×25 ml).

CAUTION: Diazomethane is **EXPLOSIVE** and **TOXIC**.

Diazomethane is also produced in the reaction of acylhydrazines with dichlorocarbene, but the process is less efficient, as only one equivalent of diazomethane is produced from two equivalents of the acylhydrazine. However, the procedure provides a useful route to symmetrical *N,N'*-diacylhydrazines (Scheme 7.25) [11].



R = Ph (49%), 2-MeC₆H₄ (46%), 3-MeC₆H₄ (41%), 4-MeC₆H₄ (45%), 4-MeOC₆H₄ (41%), 1-naphthyl (45%), 2-naphthyl (40%), benzyl (41%).

Scheme 7.25

7.6.4 Preparation of symmetrical *N,N'*-diacylhydrazines

Aqueous NaOH (40%, 1.4 mol) is added with stirring at room temperature to the acylhydrazine (0.15 mol) and TEBA-Cl (0.5 g, 2.2 mol) in CHCl_3 (75 ml, 0.95 mol). The mixture is refluxed for 30 min and then poured into ice-water (150 g). The reaction mixture is neutralized at 0°C with conc. HCl and the organic phase is separated from the precipitate. The aqueous phase and precipitate are extracted with CH_2Cl_2 (3×50 ml) and the combined organic solutions are dried (MgSO_4) and evaporated to give the diacylhydrazines.

Secondary amines

The major product isolated from the reaction of secondary amines with dichlorocarbene the reaction under phase-transfer conditions is the *N*-formylamine [12–14]. The isolated yields are considerably higher (Table 7.14) than those recorded for 'classical' procedures and are not inhibited by steric effects [15]. Diphenylamine is converted into its *N*-formyl derivative in low yield by conventional procedures and, although application of the phase-transfer catalysed procedure increases the yields, the *E*- and *Z*-1,2-bis(diphenylamino)-1,2-dichloroethenes are also obtained as by-products of the reaction [13].

TABLE 7.14
Formylation of secondary amines ($\text{R}'\text{RNH}$)

R	R'	% yield	R	R'	% yield
Et	Et	78	$-(\text{CH}_2)_5-$		54
<i>n</i> -Pr	<i>n</i> -Pr	45	Me	cyclo- C_6H_{11}	62
<i>iso</i> -Pr	<i>iso</i> -Pr	47	cyclo- C_6H_{11}	cyclo- C_6H_{11}	42
<i>n</i> -Bu	<i>n</i> -Bu	83	Me	Ph	76
<i>iso</i> -Bu	<i>iso</i> -Bu	66	Et	Ph	87
<i>t</i> -Bu	<i>t</i> -Bu	55	Ph	Ph	68
$-(\text{CH}_2)_4-$		39	$\text{CH}_2=\text{CH}-\text{CH}_2$	$\text{CH}_2=\text{CH}-\text{CH}_2$	61

It is significant that, in the case of the bis(allyl)amine, no carbene insertion into the $\text{C}=\text{C}$ bond is observed [12] (*cf.* the analogues reaction of allyl alcohols, Section 7.3). It would appear that the difference in reactivity of the amino group and the $\text{C}=\text{C}$ bond is general, as the dominant reaction of 5H-dibenzo[*b,f*]azepines with dichlorocarbene under mild conditions is the formation of the *N*-formyl derivative, and only under strongly basic conditions does further electrophilic addition to the $\text{C}=\text{C}$ bond occur [16]. Interestingly, although most cyclic amines are converted into their *N*-formyl derivatives [14], 2,2,6,6-tetrasubstituted piperid-4-one reacts preferentially at the carbonyl group [17, 18].

7.6.5 *N*-Formylation of secondary amines

The amine (0.1 mol), CHCl_3 (50 ml) and aqueous NaOH (50%, 30 ml) are stirred vigorously with TEBA-Cl (0.2 g, 0.9 mmol) at 50°C for 5 h and the mixture is then poured into H_2O (500 ml). The organic phase is separated, extracted with aqueous HCl (2%, 25 ml), washed with H_2O (2×25 ml), dried (MgSO_4), and evaporated under reduced pressure. The formamide can be purified by fractional distillation or by chromatography from silica.

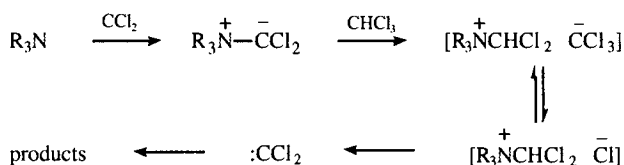
When ketones are reacted with dichlorocarbene in the presence of secondary amines, α -aminoacetamides are obtained via the ring opening of the intermediate oxiranes by the amine [19]. Similar products are obtained from the corresponding reactions with aniline and also with aldehydes (see Section 7.4).

7.6.6 Reaction between secondary amines and dichlorocarbene in the presence of ketones

Aqueous NaOH (50%, 40 ml) is added dropwise at $<5^\circ\text{C}$ to the ketone (0.2 mol), secondary amine (neat or in aqueous soln, 0.4 mol) and TEBA-Cl (1.15 g, 5 mmol) in CHCl_3 (0.3 mol) and CH_2Cl_2 (100 ml). The mixture is stirred overnight at *ca.* 5°C and worked up by the standard procedure.

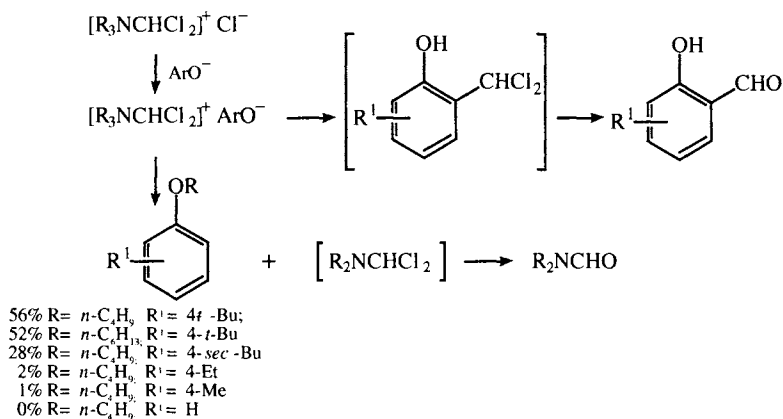
Tertiary amines

Compared with primary and secondary amines, tertiary amines are virtually unreactive towards carbenes and it has been demonstrated that they behave as phase-transfer catalysts for the generation of dichlorocarbene from chloroform. For example, tri-*n*-butylamine and its hydrochloride salt have the same catalytic effect as tetra-*n*-butylammonium chloride in the generation of dichlorocarbene and its subsequent insertion into the $\text{C}=\text{C}$ bond of cyclohexene [20]. However, tertiary amines are generally insufficiently basic to deprotonate chloroform and the presence of sodium hydroxide is normally required. The initial reaction of the tertiary amine with chloroform, therefore, appears to be the formation of the *N*-ylid. This species does not partition between the two phases and cannot be responsible for the insertion reaction of the carbene in the $\text{C}=\text{C}$ bond. Instead, it has been proposed that it acts as a lipophilic base for the deprotonation of chloroform (Scheme 7.26) to form a dichloromethylammonium ion-pair, which transfers into the organic phase where it decomposes to produce the carbene [21].



Scheme 7.26

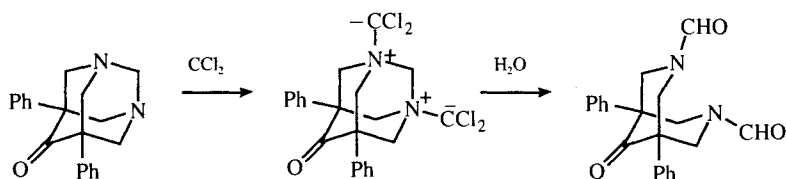
Under favourable circumstances, the initially formed *N*-ylid reacts further through C–N cleavage. Thus, in the presence of a strong nucleophile, such as a phenoxide anion, the quaternary dichloromethylammonium cation forms an ion-pair with the phenoxide anion (Scheme 7.27), which decomposes to yield the alkyl aryl ether and the *N*-formyl derivative of the secondary amine [22, 23]. Although no sound rationale is available, the reaction appears to be favoured by the presence of bulky groups at the 4-position of the aryl ring. In the absence of the bulky substituents, the Reimer–Tiemann reaction products are formed, either through the breakdown of the ion-pair, or by the more direct attack of dichlorocarbene upon the phenoxide anion [22,23].



Scheme 7.27

Use has been made of the C–N cleavage in the conversion of the bicyclic tertiary amines, derived from the $4\pi + 2\pi$ cycloaddition of pyrroles and isoindoles with benzyne, into aromatic systems, e.g. naphthalen-1,4-imines and anthracen-9,10-imines yield naphthalenes and anthracenes with the extrusion of the nitrogen bridge [24] in yields which are higher than those obtained by standard oxidation procedures.

1,3-Diazaadamantan-6-ones also undergo C–N cleavage and extrusion of (presumably) formaldehyde (Scheme 7.28) to form *N*-formyl derivatives of secondary amines [25]. The postulated mechanism indicates an initial concomitant attack of the dichlorocarbene on both nitrogen atoms but, an alternative route via the attack at one nitrogen atom, followed by ring cleavage and subsequent reaction at the

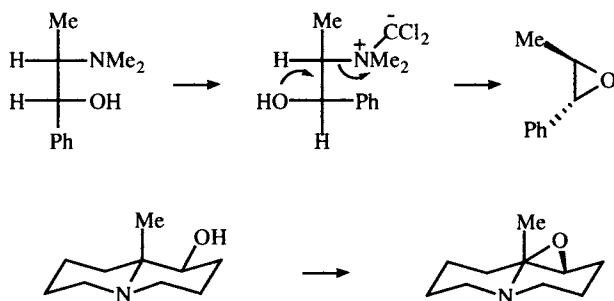


Scheme 7.28

second nitrogen atom, cannot be precluded. In no example under phase-transfer conditions has a Stevens rearrangement of the *N*-ylid and subsequent hydrolysis to give the amide been observed, although such is the case when dichlorocarbene, generated by the classical method, reacts with trialkylamines.

Predictably, the reaction of *N,N*-disubstituted enamines [26–29] and non-conjugated unsaturated amines with dihalocarbenes results in the exclusive formation of the dihalocyclopropane derivatives (see Section 7.3). Dichlorocarbene inserts into the α -CH bond of *N*-alkyldibenzo[*b,f*]azepines [16], in addition to the expected electrophilic addition to the C=C bond (see Sections 7.2 and 7.3).

Optically pure β -ethanolamines react with dichlorocarbene under phase-transfer catalytic conditions to produce epoxides of high configurational retention [30]. Initial reaction occurs at the tertiary nitrogen centre (Scheme 7.29) with subsequent cleavage of the C–N bond. The reaction is configurationally controlled, as shown by the reaction of the conformationally rigid cyclic systems; epoxide formation occurs with the equatorial hydroxyl system (50%), but not with the axial hydroxyl compound.



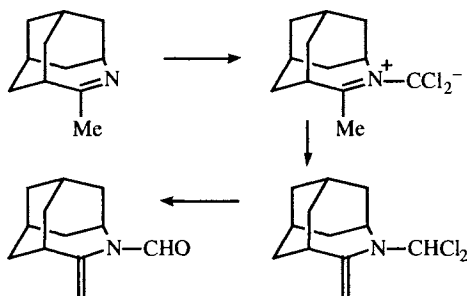
Scheme 7.29

Imines, azo compounds and oximes

The yields of dichloroaziridines, produced from imines under Makosza's phase-transfer catalytic conditions [31–35] are generally 20–30% greater than those attained by 'classical' procedures (Table 7.15). There is, however, conflicting evidence for the stabilities of the aziridines under the basic conditions. Makosza has indicated [32] that 1,3-diaryl-2,2-dichloroaziridines, derived from 4-methoxybenzaldehyde, are unstable and readily rearrange to give α -chloro- α -(4-methoxyphenyl)acetamides, whereas Graefe claims [31] to have isolated the aziridine in 90% yield. It certainly appears that the presence of an electron-withdrawing substituent on either aryl ring stabilizes the aziridine allowing its isolation in high yield under the basic conditions. Use has been made of the rearrangement of the dichloroaziridines to produce acetamides and acetimoyl chlorides as precursors for indolones [35]. The double addition of dichlorocarbene to imines derived from 1,4-diaminobenzene produces bisketene imines in high yield [33].

An interesting contrast is shown in the stabilities of the aziridines derived from the isomeric *N-tert*-butyl 2-methylpropylideneimine and *N-iso*-propyl 2,2-dimethylpropylideneimine. Solvolysis of the *N-tert*-butyl derivative occurs readily under the basic conditions, whereas the aziridine derived from the *N-iso*-propyl compound is more stable and can be isolated in 75% yield.

It is reasonable to assume that the initial step in the cycloaddition reaction is an electrophilic attack by the carbene on the nitrogen atom to form the *N*-ylid. Where proton shift is possible, cyclization does not occur and the *N*-ylid produces the *N*-formyl compound (Scheme 7.30) [36].



Scheme 7.30

7.6.7 Typical procedure for the synthesis of 1,1-dichloroaziridines

Aqueous NaOH (50%, 20 ml) is added to the imine (10 mmol) and TEBA-Cl (90 mg, 0.4 mmol) in CHCl_3 (10 ml). The mixture is stirred for 30–60 min at 40°C and then poured into H_2O (50 ml). The aqueous phase is separated and extracted with CH_2Cl_2 (3×20 ml). The combined organic solutions are washed with H_2O (2×20 ml), dried (MgSO_4), and evaporated to yield the aziridine.

Carbenes insert into the $\text{N}=\text{N}$ bond of azo compounds and the unstable adducts rearrange spontaneously to produce benzopyrazoles (e.g. Scheme 7.31) [37, 38]. The reactions of azo compounds with dichlorocarbene is also catalysed by tertiary amines [36] and, under such conditions, azoxyarenes produce the benzimidazoles, presum-

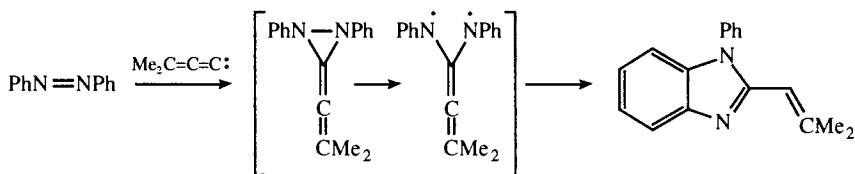
TABLE 7.15

Selected examples of the addition of dichlorocarbene to imines ($\text{R}^1\text{R}^2\text{C}=\text{NR}^3$)

R^1	R^2	R^3	% yield	R^1	R^2	R^3	% yield
Ph	H	Ph	74	Ph	Et	Ph	76
Ph	H	1-Naphthyl	72	Ph	Ph	Ph	72
Ph	H	2-Naphthyl	74	Ph	Ph	<i>p</i> - C_6H_4	62 ^a
Ph	H	PhCH_2	72				

^a bis-adduct.

ably via the initial deoxygenation of the azoxy system [39]. However, the major products (>30%) of the catalysed addition of dichlorocarbene to the azo and azoxy compounds are 1-aryl-2,2,3,3-tetrachloroaziridines, resulting from reaction of the carbene with the cleavage product, $\text{ArN}=\text{CCl}_2$ [38, 39].

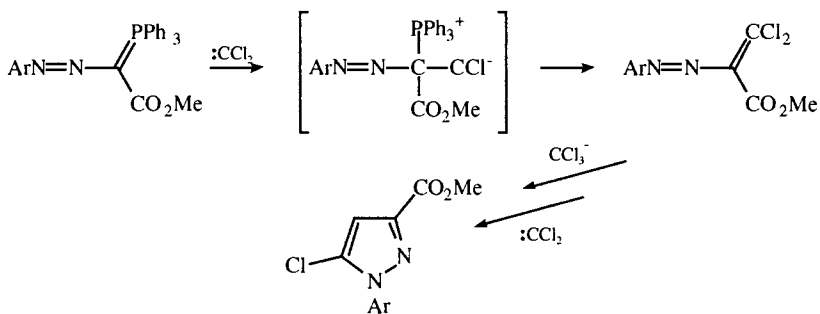


Scheme 7.31

7.6.8 2-(2-Methylpropenyl)-1-phenylbenzopyrazole

$\text{Me}_2\text{C}(\text{Cl})\text{C}\equiv\text{CH}$ (1.0 g, 10 mmol) is added with stirring at room temperature over 2.5 h to $\text{PhN}=\text{NPh}$ (2.7 g, 15 mmol) and TEBA-Cl (0.15 g, 0.65 mmol) in aqueous KOH (50%, 50 ml). The mixture is stirred at room temperature for a further 14 h and then diluted with H_2O (100 ml) and the aqueous mixture is extracted with Et_2O (3×30 ml). The dried (MgSO_4) extracts are evaporated to yield 2-(2-methylpropenyl)-1-phenylbenzopyrazole (10%).

Reaction of the azophosphoranes (Scheme 7.32) with dichlorocarbene follows an interesting pathway to produce 1-aryl-5-chloropyrazole-3-carboxylic esters. The initial displacement of the phosphine (probably as the oxide) has been confirmed by the isolation of the 3,3-dichloropropenic ester under mild conditions. Subsequent conversion into the pyrazole appears to involve reaction with a trichloromethyl anion followed by attack by a second dichlorocarbene, although evidence for the mechanism of these steps is circumstantial [40].



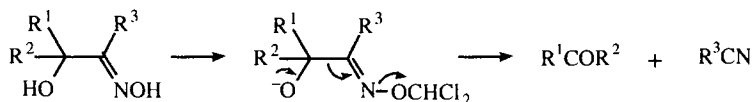
Scheme 7.32

7.6.9 Methyl 1-aryl-5-chloropyrazole-3-carboxylates

The azo compound (1 mmol) and CHCl_3 (1 ml) in CH_2Cl_2 (10 ml) are mixed with TEBA-Cl (50 mg, 2.2 mmol) in aqueous NaOH (50%, 3 ml). The mixture is stirred at room

temperature for 12 h and then diluted with H₂O (50 ml). The organic phase is separated, dried (Na₂SO₄), and evaporated to yield the pyrazole (Ar = Ph, 46%; 4-MeC₆H₄, 58%; 4-MeOC₆H₄, 57%; 2-MeOC₆H₄, 59%; 4-ClC₆H₄, 33%) (the intermediate 3,3-dichloropropenoic ester is obtained when the reaction is conducted in CHCl₃ (10 ml) at 0°C over 20 min).

Aldoximes are normally dehydrated by reaction with dichlorocarbene, produced under solid:liquid two-phase conditions, to yield nitriles in high yield [41, 42], whereas α -hydroxy ketoximes are cleaved with the simultaneous formation of a nitrile and either an aldehyde or ketone (Scheme 7.33). Yields are generally >70% and, in the case of cyclic hydroxy ketoximes, the products are acyclic oxo nitriles [43].



Scheme 7.33

7.6.10 Dehydration of aldoximes

The oxime (50 mmol) and CTMA-Br (0.36 g, 0.1 mol) are added to CHCl₃ (200 ml) and H₂O (10 ml) and stirred for 10 min. Solid KOH (14 g, 250 mmol) is added and the mixture is stirred at room temperature for a further hour. The reaction mixture is filtered and the aqueous phase is separated, extracted with CHCl₃ (2 × 20 ml), and the dried (Na₂SO₄) organic solutions are evaporated to yield the nitrile [R = Me(CH₂)₃, 80%; Me(CH₂)₅, 76%; Me(CH₂)₇, 86%; PhCH₂, 85%; Ph, 87%; 2-pyridyl, 30%; 4-pyridyl, 45%].

7.6.11 Cleavage of α -hydroxy ketoximes

Aqueous NaOH (40%, 50 ml) and TEBA-Cl (0.50 g, 2.2 mmol) are added to the hydroxy ketoxime in CHCl₃ (100 ml) and EtOAc (100 ml). The precipitate, which forms immediately, slowly dissolves as the mixture is heated under reflux for 30 min. When the reaction is complete, as shown by TLC analysis, the organic phase is separated, washed with HCl (2M, 5 ml) and H₂O (10 ml), dried (Na₂SO₄), and evaporated to yield the cleavage products (70–80%), which can be purified by chromatography.

Amides and related compounds

Amides [41, 44], thioamides [41] and amidines [45] are converted into nitriles by the reaction with dichlorocarbenes generated by Makosza's procedure (Table 7.16). Under similar conditions, monosubstituted and *N,N*-disubstituted ureas are converted into cyanamides (Table 7.17); *N,N*'-disubstituted ureas produce carbodiimides in low yield [41, 46, 47]. *N*-Carbamoyl derivatives of dibenzo[*b,f*]diazepines and the related 10,11-oxirane derivatives are converted into the corresponding

TABLE 7.16
Selected examples of the synthesis of nitriles

RCN	From amide	% yield	
		from thioamide	From amidine
R = Me	—	—	61 ^a
Et	45 ^a	—	84 ^a
<i>n</i> -Pr	55 ^b	—	—
<i>iso</i> -Pr	94 ^b	—	90 ^a
<i>tert</i> -Bu	89 ^b	—	—
<i>n</i> -C ₅ H ₁₁	95	—	—
PhCH ₂	75	—	—
cyclo-C ₆ H ₁₁	95	—	—
Ph	85	67	92
4-ClC ₆ H ₄	79	—	85
4-MeOC ₆ H ₄	—	—	78
4-NO ₂ C ₆ H ₄	40	—	—
PhCH=CH	52	—	—
2-Mefur-3-yl	80	—	—

^a Estimated by GLC analysis. ^b Estimated by NMR analysis.

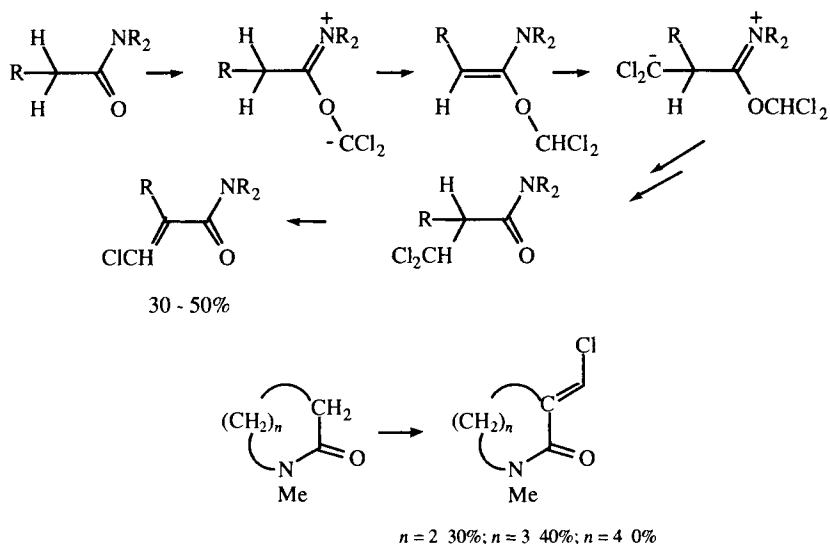
N-cyano compounds under mild conditions, but prolonged exposure of the azepine to an excess of the reagent results in further reaction to produce the cyclopropane derivative [41].

In isolated examples, reactions of specific amides and thioamides with dihalocarbenes can take unusual pathways. Thus, for example, using procedure 7.1.1, *N,N*-dialkylamides are converted into α -chloromethylene derivatives of the amides [48]. The initial step in which the carbene attacks the carbonyl oxygen atom is the same as for the dehydration of the *N*-alkyl amides, but subsequent steps, for which there is evidence from ²H/¹H labelling experiments, lead to the formation of an enamine and further reaction with the carbene (Scheme 7.34).

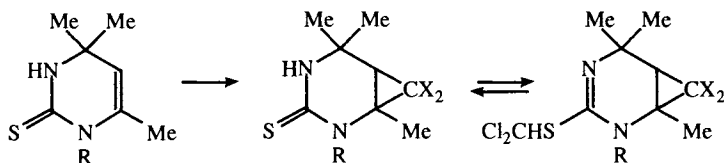
1-Substituted 4,4,6-trimethyl-1,4-dihydropyrimidine-2(3*H*)-thiones behave as enamines [49] to yield dichlorocyclopropanes (Scheme 7.35). Further reaction

TABLE 7.17
Selected examples of the conversion of *N,N*-disubstituted ureas into cyanamides

R ¹	R ²	% yield of R ¹ R ² NCN	R ¹	R ²	% yield of R ¹ R ² NCN
<i>i</i> -Pr	H	40	<i>n</i> -C ₅ H ₁₁	<i>n</i> -C ₅ H ₁₁	50
<i>n</i> -Bu	H	20	-(CH ₂) ₄ -		75
<i>n</i> -C ₅ H ₁₁	H	31	-(CH ₂) ₅ -		65
Me	Me	30	-(CH ₂) ₂ O(CH ₂) ₂ -		45
Et	Et	45	-(CH ₂) ₂ NPh(CH ₂) ₂ -		50
<i>i</i> -Pr	<i>i</i> -Pr	60	PhCH ₂	PhCH ₂	85
<i>n</i> -Bu	<i>n</i> -Bu	55	Ph	Me	70



Scheme 7.34



Scheme 7.35

occurs on the thione group but, as cleavage of the thioamide system is energetically unfavourable, prototropic shift results in the formation of the dichloromethylthioether. On heating, or under basic conditions, the thioether reverts to the thione. Under similar conditions, dibromocarbene produces the dibromocyclopropane, together with 1-substituted 4,4,6-trimethyl-1,4-dihydropyrimidin-2(3*H*)-one, which presumably results from the base-catalysed decomposition of the dibromomethylthioether or the zwitterionic precursor. Diiodocarbene produces only the dihydropyrimidin-2(3*H*)-one. Neither of the two nitrogen atoms reacts with the carbenes.

Azides

Dichlorocarbene reacts exothermically under solid:liquid two-phase conditions with azides to produce, initially, isocyanide dichlorides, $RN=CCl_2$, which can react further to give *N*-alkyltetrachloroaziridines [50]. The aziridines are the major products (60–70%) with simple alkyl azides, but the reaction tends to stop at the isocyanide step (50–60%), when the alkyl group is highly fluorinated.

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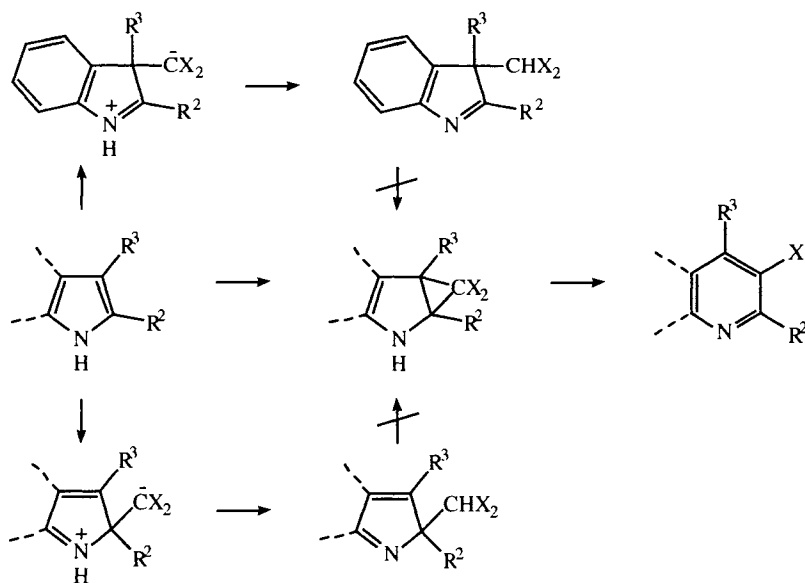
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7.7 REACTIONS WITH HETEROAROMATIC COMPOUNDS

The reactivity of heterocyclic systems with carbenes, generated under phase-transfer catalytic conditions, has been reviewed for the period up to 1983 [1]. Most unsaturated non-heteroaromatic systems react with carbenes in the manner expected of alkenes, amines, amides, ketones, etc. (see Sections 7.3, 7.5 and 7.6).

The Reimer-Tiemann reaction in which dichlorocarbene reacts with π -electron excessive aromatic systems to yield aryl aldehydes is singularly inefficient for the synthesis of 2-formylpyrroles and 3-formylindoles [2]. Instead, ring expansion normally occurs to produce 3-chloropyridines and 3-chloroquinolines, respectively. The reaction conditions and the mechanism have been studied extensively [2–4] and it has been shown that the choice of solvent and base plays a critical role in the course of the reaction. Under mildly basic phase-transfer catalytic conditions, the major products are the ring expanded heteroarenes [5, 6] (Scheme 7.36). A similar sequence of addition and rearrangement reactions are observed between dimethylvinylidene carbene and methylpyrroles leading to, among other products, 3-vinylpyridines [7]. Ring expansion also occurs in the reaction between 3-methylindole and adamantylidenevinylidene carbene to produce the predicted quinoline [8].



Scheme 7.36

TABLE 7.18

Selected examples of the reaction of pyrroles and indoles with dihalocarbenes

Azole	Carbene	Method	Product	% yield
2,5-Dimethylpyrrole	CCl ₂	7.7.1.A	3-Chloro-2,6-dimethylpyridine	49 ^a
2,3,4,5-Tetramethylpyrrole	CCl ₂	7.7.1.A	3-Chloro-2,4,5,6-tetramethylpyridine	37 ^b
3-Methylindole	CCl ₂	7.7.1.A	3-Chloro-4-methylquinoline	68 ^c
	CBr ₂	7.7.1.B	3-Bromo-4-methylquinoline	24
	CFCI	7.7.1.C	3-Chloro-4-methylquinoline	6 ^d
			3-Fluoro-4-methylquinoline	6
2-Methylindole	CCl ₂	7.7.1.B	3-Chloro-2-methylquinoline	45
2-Phenylindole	CCl ₂	7.7.1.B	3-Chloro-2-phenylquinoline	47
2,3-Dimethylindole	CCl ₂	7.7.1.A	3-Chloro-2,4-dimethylquinoline	63 ^{ef}
	CFCI	7.7.1.C	3-Chloro-2,4-dimethylquinoline	~1
			3-Fluoro-2,4-dimethylquinoline	32 ^g
1,2,3-Trimethylindole	CFCI	7.7.1.C	3-Chlorofluoromethyl-1,3-dimethyl-2-methyleneindolene	^h

^a + 7% 2-dichloromethyl-2,5-dimethyl-2*H*-pyrrole. ^b + 44% 2-dichloromethyl-2,3,4,5-tetramethyl-2*H*-pyrrole. ^c 53% using method 7.7.1.B. ^d + 2% 3-chlorofluoromethyl-3-methyl-3*H*-indole and 10% 1-formyl-3-methyl-indole. ^e + 15% 3-dichloromethyl-2,3-dimethyl-3*H*-indole. ^f 55% using method 7.7.1.B. ^g + 18% 3-chlorofluoromethyl-2,3-dimethyl-3*H*-indole. ^h Labile product. No yield recorded.

Analogous reactions with bromoform produces the corresponding 3-bromo derivatives [6], while the reaction of alkylindoles with chlorofluorocarbene produces a complex mixture of halogenated heterocycles (Table 7.18) [9].

7.7.1 Reactions of pyrroles and indoles with dihalocarbenes

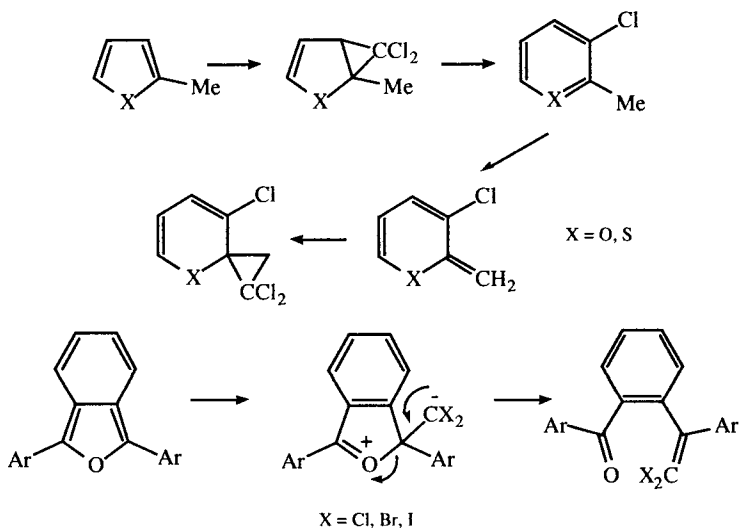
Method A: Aqueous NaOH (50%, 6 ml) is added dropwise over a period of 15 min to the azole (10 mmol) and TEBA-Cl (0.05 g, 0.2 mmol) in CHCl₃ (1.5 ml) and PhH (1.5 ml) at 40°C (3.2 ml of CHCl₃ with no PhH can be used with pyrroles). The two-phase system is stirred for 8 h (polyalkylpyrroles require only *ca.* 2 h) and then diluted with Et₂O (20 ml). The organic solution is extracted with aqueous HCl (2M, 3 × 15 ml) and the acidic extracts are neutralized with aqueous NaOH (5M). The aqueous solution is extracted with Et₂O (3 × 20 ml) and the combined extracts are dried (Na₂SO₄) and evaporated. The crude product is purified by chromatography on silica.

Method B: Aqueous NaOH (33%, 5 ml) is added with stirring to the azole (7.5 mmol) and TEBA-Cl (0.173 g, 0.75 mmol) in CHCl₃ or CHBr₃ (10 ml) at 0°C. The mixture is stirred at 0°C for 6 h and then at room temperature for 24 h. The aqueous layer is separated and extracted with CHCl₃ (2 × 15 ml). The organic solutions are extracted with aqueous HCl (20%, 3 × 30 ml) and the combined extracts are neutralized with aqueous NaOH (10%) and further extracted with CHCl₃ (3 × 25 ml). The dried (Na₂SO₄) organic extracts are evaporated to yield the azine.

Method C: The azole (0.5 mol) and TEBA-Cl (0.23 g, 1 mmol) in CH₂Cl₂ (15 ml) are mixed with aqueous NaOH (50%, 20 ml) at 0°C and the mixture is stirred for 1–2 h. CHCl₂F in CH₂Cl₂ (*ca.* 50%, 33 ml) is then added dropwise. The two-phase system is stirred at room temperature for 12 h and the product is isolated as described in 7.7.1.A.

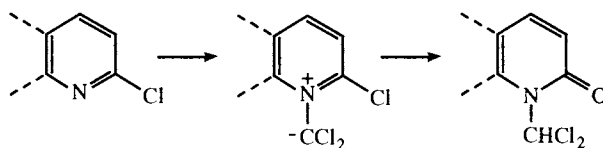
1,2,3,4-Tetrahydrocarbazole reacts with dichlorocarbene to form (4a-dichloromethyl)-2,3,4,4a-tetrahydro-1*H*-carbazole (22%) and its *N*-formyl derivative (15%), together with bis(1,2,3,4-tetrahydrocarbazol-9-yl)methane (12%) [10].

2-Methylfuran and 2-methylthiophene react with dichlorocarbene in a similar manner (7.7.1.B), but the initially formed six-membered ring system reacts further to produce labile spiro cyclopropyl derivatives (Scheme 7.37) in extremely low yields (< 3%). The stabilizing effect of the benzo[*b*] derivative improves the yield to 38% [11]. Benzo[*c*]furan reacts extremely rapidly (1–20 min) with the halocarbene to produce ring-opened adducts [12] in high yield (>90%). It has been argued that the mechanism involves an initial 1,2-addition to the furan ring [12], but a direct electrophilic attack at the α -position of the furan ring, driven by regeneration of the benzenoid character of the benzo group, is an equally plausible mechanism (Scheme 7.37).



Scheme 7.37

In contrast with the azoles, diazoles and their benzo derivatives tend to react with dichlorocarbene to yield the tris(diazolyl)methanes, presumably via the initial formation of the *N*-dichloromethyl derivative [6, 13]. Only in more activated polymethyl derivatives does reaction occur at a ring carbon atom. In a similar manner (7.7.1.B), 2-chloropyridine and 2-chloroquinoline react with dichlorocarbene at the ring nitrogen atom to yield, after nucleophilic displacement of the chloro group, the 1-dichloromethyl-2-oxo derivatives (13–25%) [14] (Scheme 7.38). 2-Chlorobenzothiazole reacts in an analogous manner, but other pyridine and quinoline derivatives fail to react. It is also noteworthy that the dichloromethyl group is unusually stable and is not converted into the formyl group.



Scheme 7.38

7.7.2 Reaction of diazoles with dihalocarbenes (Table 7.19)

Method A: The diazole (0.05 mol) and TEBA-Cl (0.23 g, 1 mmol) in CHCl_3 (16 ml, 0.2 mol) or CHBr_3 (8.7 ml, 0.1 mol) are mixed at 0°C with NaOH (10 g) in H_2O (10 ml). The two-phase system is stirred for 4–6 h at 0°C and then at room temperature for 12 h (should the mixture become viscous, CH_2Cl_2 (ca. 30 ml) is added). The mixture is extracted with Et_2O (2×20 ml) and CH_2Cl_2 (2×20 ml), and the combined extracts are dried (Na_2SO_4) and evaporated. The crude products are separated and purified by chromatography on Kieselgel.

Method B: The diazole (0.05 mol), powdered $\text{CCl}_3\text{CO}_2\text{Na}$ (18.5 g, 0.1 mol) and Aliquat (0.5 g, 1 mmol) in CHCl_3 (50 ml) are warmed at 60°C for 10–15 h until the evolution of CO_2 ceases. The black mixture is filtered, evaporated under reduced pressure, and the products are isolated by chromatography on Kieselgel.

Method C: Aqueous NaOH (50%, 8 ml) is added to the diazole (10 mmol) and alkyl (C_{17-37}) benzyltrimethylammonium chloride (40 mg) in PhH (12 ml), and the mixture is heated to 50°C . CHCl_3 (4 ml) in PhH (4 ml) is added dropwise with stirring over 30 min. Brine (20 ml) is added to the two-phase system, which is then extracted with Et_2O (4×25 ml). The dried (Na_2SO_4) organic extracts are evaporated under reduced pressure and the products are isolated by chromatography on silica.

TABLE 7.19

Selected examples of the reaction of diazoles with dichlorocarbene

Diazole	Method	Product	% yield
Imidazole	7.7.2.B	Trisimidazol-1-ylmethane	4
2-Methylimidazole	7.7.2.A	Tris(2-methylimidazol-1-yl)methane	6
2,4,5-Trimethylimidazole	7.7.2.C	5-Chloro-2,4,6-trimethylpyrimidine	39
3,4,5-Trimethylpyrazole	7.7.2.C	Tris(3,4,5-trimethylpyrazol-1-yl)methane	63 ^a
Benzimidazole	7.7.2.A	Tris(benzimidazol-1-yl)methane	4 ^b
2-Methylbenzimidazole	7.7.2.B	Tris(2-methylbenzimidazol-1-yl)methane	14

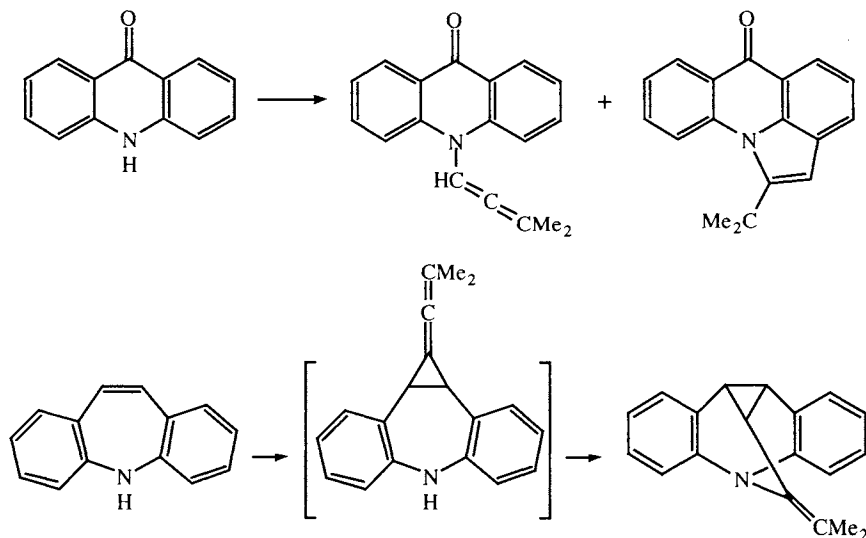
^a + 2.7% 4-chloro-3,5,6-trimethylpyridazine and 3.2% 3-dichloromethyl-2,3,4-trimethyl-3H-pyrazole. ^b Also obtained with :CClF using method 7.7.1.C.

Not surprisingly, when the aromaticity of thiophene is destroyed by the formation of the *S,S*-dioxide, the ring reacts readily with chloroform and bromoform under basic catalytic conditions. However, instead of forming the insertion adduct, the major product isolated in each case is the 3-(dihalomethylene)-2,3-dihydrothiophene-*S,S*-dioxide via initial reaction with the trihalomethyl anions [15].

7.7.3 One-pot synthesis of thiophene *S,S*-dioxide and reaction with trihalomethyl anions

TEBA-Cl (0.1 g, 0.44 mmol) in aqueous NaOH (50%, 75 ml) is added to 3,4-dibromo-2,3,4,5-tetrahydrothiophene *S,S*-dioxide (5 g, 18 mmol) in the CHCl_3 (100 ml), or CHBr_3 (20 ml), and CH_2Cl_2 (80 ml). The mixture is stirred for 90 h at room temperature and CH_2Cl_2 (100 ml) and H_2O (300 ml) are then added. The organic phase is separated, washed with H_2O (50 ml), dried (MgSO_4), and evaporated to yield the 3-(dihalomethylene)-2,3-dihydrothiophene *S,S*-dioxide (chloro compound, 26%; bromo compound, 53%).

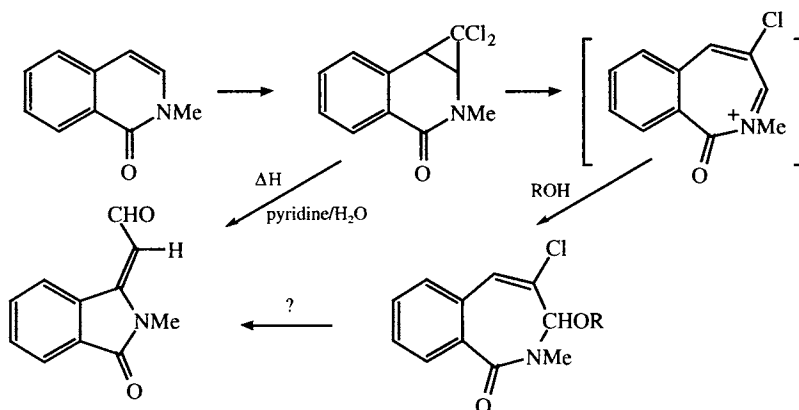
Both acridone and dibenzo[*b,f*]azepine produce unexpected products (Scheme 7.39) when reacted with dimethylvinylidene carbene (**7.1.18.A**). Acridone reacts initially at the nitrogen atom to produce the 10-(3,3-dimethylallenyl) derivative (13%) and a pyrroloacridone (10%) which, if the structure is correct, could be derived from the allene by sigmatropic shifts [16]. The dibenzoazepine reacts as expected to produce a cyclopropyl derivative but, under the reaction conditions, the adduct rearranges spontaneously to yield a 1,6-methanodibenzo[*b,f*]cycloprop [*d*]azepine, the structure of which was confirmed by X-ray crystallography [17].



Scheme 7.39

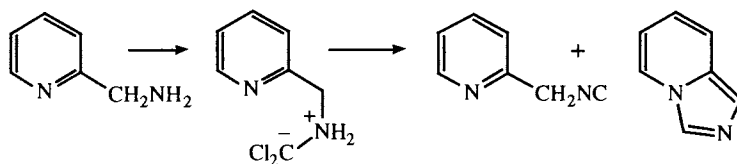
2-Methylisoquinol-1-one behaves as an enamine with dichlorocarbene to produce the dichlorocyclopropane derivative (83%). The corresponding reaction with dibromocarbene produces a thermally labile compound, which is assumed to have an analogous structure. Rearrangement of the dichloro compound under basic conditions leads to the isoindole derivative (96%), whereas controlled thermolysis

produces the oxoazepinium ion, which can be trapped as the 3-alkoxy derivative upon treatment with alcohols [18] (Scheme 7.40).



Scheme 7.40

In the reaction of dichlorocarbene with 2-aminomethylpyridine the initial reaction is, as expected, with the amino group. Subsequent solvolysis and cyclization produces the imidazo[1,5-*a*]pyridine (25%) [19], although a considerable amount of tar is also formed. A significant by-product of the reaction is 2-pyridylmethyl isocyanide suggesting the mechanism shown in Scheme 7.41. Similar cyclizations to the fused imidazo products were obtained with 2-aminomethylquinolines (20–24%) and 1-aminomethylisoquinoline (32%), but the corresponding reaction with 3-aminomethylisoquinoline failed.



Scheme 7.41

7.7.4 Imidazo[1,2-*a*]pyridine and related compounds

Aqueous NaOH (40%, 20 ml) is added to the aminomethylazine (9.7 mmol), TPA-Br (53 mg, 9.7 mmol) and CHCl_3 (2 ml) in *n*-PrOMe (1.5 ml) and the mixture is stirred at 50°C for *ca.* 4.5 h. When the reaction is complete, as shown by TLC analysis, CH_2Cl_2 (50 ml) is added and the mixture is washed with H_2O (2×30 ml). The washings are extracted with CH_2Cl_2 (3×30 ml) and the dried (Na_2SO_4) organic solutions are evaporated and to give the fused imidazole, which is purified by chromatography on silica.

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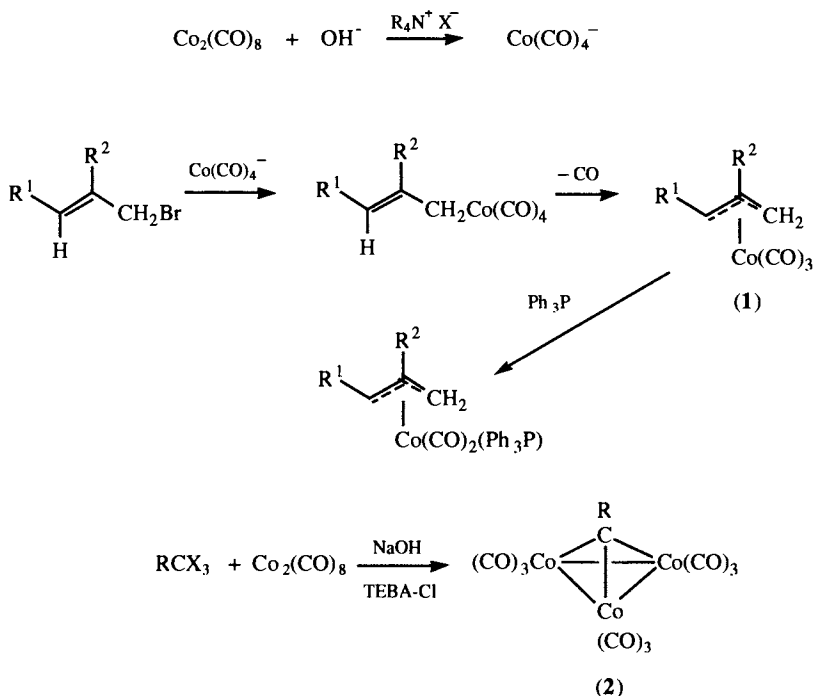
Carbonylation and Other Reactions

8.1 INTRODUCTION

A comparatively recent and extremely valuable extension of phase-transfer catalysis is to be found in its application to the chemistry of metal carbonyls, which crosses the boundaries of inorganic chemistry, through organometallic chemistry, and into organic chemistry.

The basic chemistry of transition metal carbonyls has been reviewed extensively [1–3] and many of the procedures, which are of value in synthetic organic chemistry, have been reported to be frequently tedious and invariably involve prolonged reaction times, high temperatures, and high pressures of carbon monoxide. The first significant reports of the use of phase-transfer catalysis with metal carbonyls describes the simple *in situ* formation of the cobalt tetracarbonyl anion from dicobalt octacarbonyl and its subsequent use in the preparation of π -allylcobalt tricarbonyl complexes (1) and of alkylidyne tricobalt nonacarbonyl complexes (2) [4]. Benzyltriethylammonium chloride catalyses the interfacial reaction between the dicobalt octacarbonyl, which is soluble in the organic phase, and aqueous sodium hydroxide to form the $\text{Co}(\text{CO})_4^-$ anion. The anion, being a relatively ‘soft’ base, forms a stable ion pair with the quaternary ammonium cation and diffuses into the bulk of the organic phase where nucleophilic reaction with the allyl halide initially produces the π -cobalt compound and, subsequently, with loss of carbon monoxide, the π -allylcobalt complex, which is isolated as a more stable triphenylphosphine derivative (Scheme 8.1). Kinetic studies indicate that the conversion of the dicobalt octacarbonyl into the cobalt tetracarbonyl anion at room temperature and the subsequent formation of the π -allyl complex is complete within 15 minutes. In the absence of the phase-transfer catalyst, no π -allyl complex is formed.

In a similar manner, π -allyl complexes of manganese, iron, and molybdenum carbonyls have been obtained from the corresponding metal carbonyl halides [5]. In the case of the reaction of dicarbonyl(η^5 -cyclopentadienyl)molybdenum bromide with allyl bromide, the σ -allyl derivative is obtained in 75% yield in dichloromethane, but the π -allyl complex is the sole product (95%), when the reaction is conducted in a water:benzene two-phase system. Similar solvent effects are observed in the corresponding reaction of the iron compound. As with the cobalt tetracarbonyl anion, it is



Scheme 8.1

postulated that the σ -allyl system is initially formed, but the conversion into the π -complexes generally requires photolytic or thermal conditions [6, 7] in excess of those normally encountered in the phase-transfer catalysed reactions. The overall reaction for the formation of the π -allyl metal carbonyl complexes, which takes place in the organic phase, can be rationalized by the mechanism depicted in Scheme 8.1, but the cause of the specificity of the solvent effect is, as yet, unclear and attempts to convert the σ -allyl compounds into the π -allyl system under phase-transfer conditions in benzene have failed, even upon the further addition of allyl bromide [7].

The alkylidyne tricobalt nonacarbonyl complexes (2) are produced from the reaction of the cobalt tetracarbonyl anion with 1,1,1-trihaloalkanes [4], under conditions analogous to those used for the synthesis of the π -allyl complexes. Although the yields for (2) appear to be low (Table 8.3), they are better than, or comparable with, those obtained by the traditional procedures [8] and are obtained under more amenable conditions.

In a one-pot process for the preparation of the complexes from cobalt(II) nitrate, which is converted into the tetracarbonyl anion by the standard procedure [9], higher yields of (2) are claimed ($\text{R} = \text{Cl}$, 42%; $\text{R} = \text{Br}$, 36%; $\text{R} = \text{H}$, 30%) using cetyltrimethylammonium bromide as the catalyst. It is known that the cluster compounds are unstable under basic conditions and it was noted that, for example, in the preparation of the chloro compound, extended reaction times (4.5 hours) resulted in the total decomposition of the product [10].

8.1.1 General preparation of π -allyl cobalt tricarbonyl complexes (Scheme 8.1)

The allyl bromide (1.0 mmol) is added with stirring under N_2 to TEBA-Cl (0.11 g, 0.5 mmol) and $Co_2(CO)_8$ (0.17 g, 0.5 mmol) in aqueous NaOH (5M, 10 ml) and PhH (10 ml). The mixture is stirred at room temperature (Table 8.1) and the organic phase is then separated, dried ($MgSO_4$), and evaporated to give the π -allyl complex. The complex is redissolved in a minimum amount of PhH to which is added an equimolar amount of Ph_3P to yield the π - $C_3H_5Co(CO)_2(Ph_3P)$ complex.

TABLE 8.1
Formation of π -allyl cobalt complexes

R ¹	R ²	Reaction time	% yield
H	H	15 min	80
H	Me	40 min	73
Me	H	15 min	80
Ph	H	1 h	72

8.1.2 Synthesis of allyl complexes of Fe, Mn and Mo

Method A: TEBA-Cl (0.33 g, 1.5 mmol) in aqueous NaOH (5M, 45 ml) is added with stirring to $CH_2=CHCH_2Br$ (1.8 g, 15 mmol) and the metal carbonyl halide (3 mmol) in PhH or CH_2Cl_2 (10 ml). The mixture is stirred at room temperature for *ca.* 20 min and then worked up and converted into the triphenylphosphine derivative by the procedure described in 8.1.1.

Method B: The metal carbonyl halide (1 mmol) in PhH (15 ml) is added slowly with stirring to TEBA-Cl (1.1 g, 5 mmol) and the allyl bromide (1.2 g, 10 mmol) in a two-phase system of PhH (15 ml) and aqueous NaOH (5 M, 20 ml). The complex is isolated using the procedure given in 8.1.2.A.

TABLE 8.2
 π -Allyl complexes of Fe, Mn, and Mo

Metal carbonyl halide	Method (solvent)	Reaction time	% yield
$Mn(CO)_3Br$	8.1.2.A (CH_2Cl_2)	5 h ^a	80 ^b
$Mn_2(CO)_8Cl_2$	8.1.2.A (PhH)	1 h	40
$Mn(CO)_4Ph_3PBr$	8.1.2.A (CH_2Cl_2)	1 h ^a	90
π - $C_3H_5Fe(CO)_3Br$	8.1.2.A (PhH)	1 h	76 ^c
$CpMo(CO)_3Cl$	8.1.2.B (PhH)	8 h ^d	95 ^e
$CpFe(CO)_2Br$	8.1.2.B (PhH)	4 h	60 ^f

^a Under reflux. ^b 60% after 4 h at 60 °C in PhH. ^c bis π -complex. ^d At 45 °C. ^e σ -complex formed in 75% yield in CH_2Cl_2 after 5 h at rt. ^f σ -complex formed in 36% yield in CH_2Cl_2 after 2 h at rt using 8.1.2.A.

8.1.3 Preparation of alkylidyne tricobaltnonacarbonyls (Table 8.3)

Method A: Aqueous NaOH (5M, 15 ml) is added with stirring under N₂ to the 1,1,1-trichloroalkane (1.0 mmol), Co₂(CO)₈ (1.0 g, 3.0 mmol) and TEBA-Cl (0.1 g, 0.4 mmol) in PhH (20 ml). The mixture is stirred at room temperature for 45 min to 2.5 h (to prevent decomposition of the product, as short a time as possible should be used) and the organic phase is then separated, washed with H₂O (3 × 20 ml) and dried (MgSO₄). The product is isolated by evaporation of the solvent and purified by sublimation or chromatography on silica.

Method B: Co(NO₃)₂·6H₂O (8.7 g, 30 mmol) in aqueous NH₃ (12%, 200 ml) is reduced with an excess of Na₂S₂O₃ under an atmosphere of CO. PhH (100 ml), the 1,1,1-trihaloalkane (30 mmol), and CTA-Br (0.25 g, 0.7 mmol) are added and the mixture is stirred for *ca.* 45 min (90 min in the case of CCl₄). The purple PhH phase is separated, dried (MgSO₄), and evaporated to yield the complex.

TABLE 8.3
Alkylidyne tricobalt nonacarbonyls from trihaloalkanes

RCX ₃		Reaction conditions	% yield
R =	Cl	X = Cl	42
	Br	Br	11
	Ph	Cl	53
	CO ₂ CMe ₃	Cl	30
	CH ₂ OH	Cl	trace

^a Using 3M NaOH.

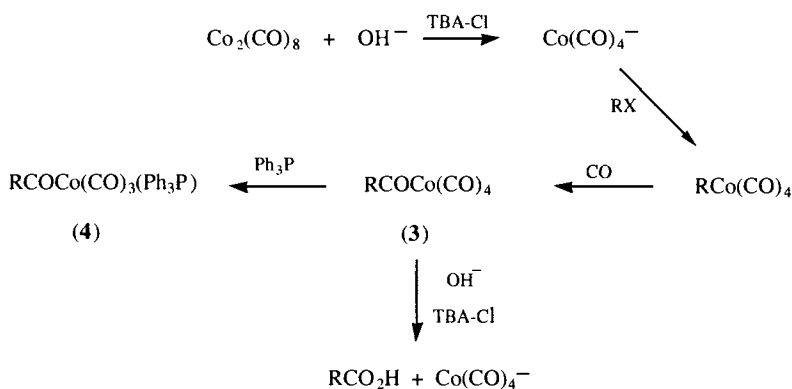
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8.2 CARBONYLATION REACTIONS LEADING TO ALIPHATIC CARBOXYLIC ACIDS, ESTERS, LACTONES AND CARBOXAMIDES

An extension of the facile formation of the σ -allylcobalt carbonyl compounds provides the basis for the conversion of alkyl and aryl halides into ketones and

carboxylic acids. Haloalkanes react with NaCo(CO)_4 [1] or with KCo(CO)_4 in a two-phase system in the presence of tetra-*n*-butylammonium chloride, or with the cobalt tetracarbonyl anion, produced *in situ* from dicobalt octacarbonyl [2, 3]. Under an atmosphere of carbon monoxide, the alkylcobalt tetracarbonyl complexes are converted (Scheme 8.2) into the corresponding acyl derivatives (3), which are unstable under the alkaline conditions but, if prepared under neutral phase-transfer conditions from the preformed cobalt tetracarbonyl anion, they can be converted into the more stable triphenylphosphine complexes (4) e.g. $\text{R} = \text{PhCH}_2$ [4].



Scheme 8.2

Kinetics show that the reaction is pseudo-first order in the RX concentration and that there is a linear correlation in the rate of consumption of RX with the concentration of the catalyst. The need for a high rate of stirring indicates that, as discussed in Chapter 1, the base-initiated formation of the cobalt tetracarbonyl anion results from an 'interfacial exchange' process. It is significant that, when preformed NaCo(CO)_4 is used, the extractability of the anion by benzyltriethylammonium cation into diisopropyl ether is three times less efficient than it is into benzene or dichloromethane, but kinetic studies show that, in spite of the lower concentration of the anion in the ether, the rate of reaction with RX in that solvent is generally higher [3].

Phase-transfer catalysed formation of the acylcobalt tricarbonyl complexes using a polymer-supported ammonium salt produces lower yields of the complexes [4].

8.2.1 Preparation of acylcobalt tricarbonyl triphenylphosphine complexes

The haloalkane (2.0 mmol) is added with stirring at 20°C to NaCo(CO)_4 (0.39 g, 2.0 mmol) and TBA-Cl (28 mg, 0.1 mmol) in a H_2O (25 ml): CH_2Cl_2 (25 ml) system. The mixture is stirred (1100 r.p.m.) for *ca.* 45 min under CO (1 atmos.). The organic phase is then separated, washed with H_2O (3×25 ml), and dried (MgSO_4). Addition of Ph_3P (0.52 g, 2.0 mmol) and evaporation of the solvent yields the tricarbonyl triphenylphosphine complexes, $\text{RCH}_2\text{COCO(CO)}_3(\text{Ph}_3\text{P})$ (e.g. $\text{R} = \text{H}$, 36%; Ph , 44%; 4- BrC_6H_4 , 42%; 2,4,6- $\text{Me}_3\text{C}_6\text{H}_2$, 38%; 3- CNC_6H_4 , 57%; 2- MeC_6H_4 , 51%; 2-naphthyl, 35%; $\text{CH}_2\text{CO}_2\text{Me}$, 27%).

A second interfacial exchange reaction of the σ -acylcobalt complex with hydroxide ion leads to the production of the alkanecarboxylate anion, which migrates into the aqueous phase, leaving the cobalt tetracarbonyl anion in the organic phase for subsequent reaction (Scheme 8.2). Optimum yields of the carboxylic acids are obtained with *ca.* 40:1 ratio of the alkyl halide to dicobalt octacarbonyl. $\text{Co}(\text{Ph}_3\text{P})_2\text{Cl}_2$ can also be used and has the advantage that the cobalt can be recycled easily [5].

Benzyltriethylammonium chloride is frequently used as the phase-transfer catalyst, but it has been noted that the catalyst itself produces phenylacetic acid under the carbonylation conditions [6]. Trimethyl(phenyl)ammonium chloride and tetra-*n*-butylammonium chloride both catalyse the reaction efficiently.

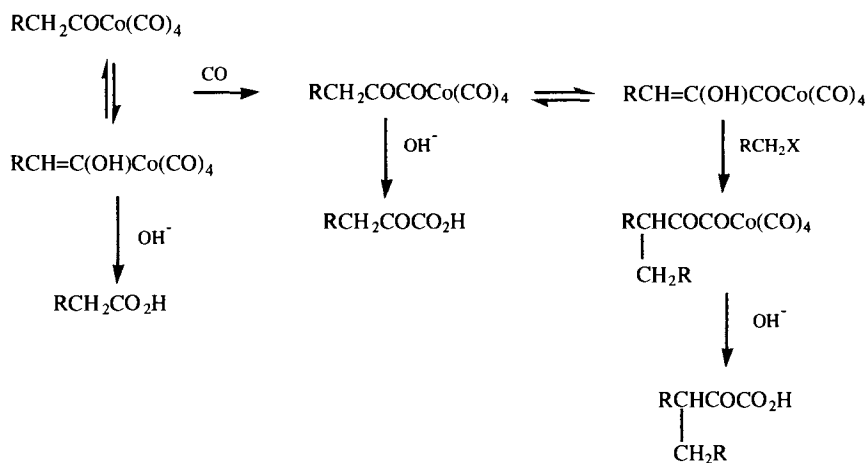
Although a wide range of arylacetic acids have been obtained by this procedure in generally good yields [7–9], there can be significant side-reactions. Of major importance is the double carbonylation reaction, which produces pyruvic acid derivatives [2, 10–12]. This reaction occurs frequently under high pressures of carbon monoxide (>1 atmos.) [9]. Also, although too few examples have been cited, in the case of reactions with benzyl halides, substitution on the aryl ring by electron-donating groups also favours double carbonylation [8] (Table 8.4). Further *C*-alkylation of the pyruvic acid may also occur, although steric factors inhibit the reaction.

Not unexpectedly, alkylation of the double carbonylated complex proceeds via a base-catalysed interfacial enolization step, but it is significant that the initial double carbonylation step also involves an interfacial reaction, as it has been shown that no pyruvic acid derivatives are obtained at low stirring rates. Further evidence comes from observations of the cobalt-catalysed carbonylation of secondary benzyl halides [8], where the overall reaction is more complex than that indicated by Scheme 8.3. In addition to the expected formation of the phenylacetic and phenylpyruvic acids, the reaction with 1-bromo-1-phenylethane also produces 3-phenylpropionic acid, 2,3-diphenylbutane, ethylbenzene and styrene (Scheme 8.4). The absence of secondary carbonylation of the phenylpropionylcobalt tetracarbonyl complex is consistent with the less favourable enolization of the phenylpropionyl group, compared with the phenylacetyl group.

TABLE 8.4

Selected examples of the conversion of benzyl chlorides into arylacetic acids and arylpyruvic acids using molybdenum carbonyl complexes

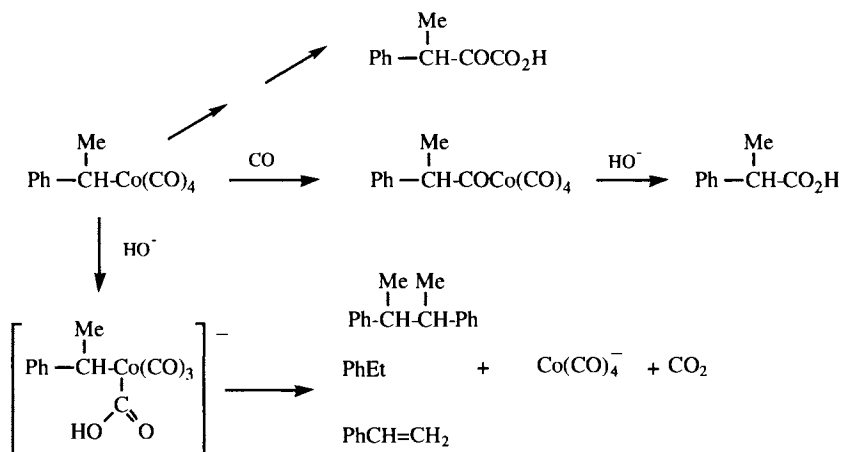
ArCH_2Cl	% overall yield of acids	% ratio		
		$\text{ArCH}_2\text{CO}_2\text{H}$	$\text{ArCH}_2\text{CO}_2\text{CO}_2\text{H}$	$\text{ArCH}_2\text{CH}(\text{Ar})\text{CO}_2\text{CO}_2\text{H}$
$\text{Ar} = \text{Ph}$	60	100	0	0
2-MeC ₆ H ₄	78	60	0	40
3-MeC ₆ H ₄	58	82	0	18
4-MeC ₆ H ₄	75	70	0	30
2,4,6-Me ₃ C ₆ H ₂	21	50	50	0
3-CNC ₆ H ₄	34	100	0	0



Scheme 8.3

A high carbon monoxide pressure (~5 atmos.) favours the formation of the butane. Possible mechanisms for its formation include homolytic cleavage of the benzylcobalt tetracarbonyl complex and recombination of the radicals to generate 2,3-diphenylbutane and dicobalt octacarbonyl, or a base-catalysed decomposition of the benzylcobalt tetracarbonyl complex (Scheme 8.4). The ethylbenzene and styrene could arise from the phenylethyl radical, or from the π -styrene hydridocobalt tricarbonyl complex.

Analogous carbonylation reactions using nickel and iron carbonyl based systems also produce alkanecarboxylic acids [11, 13, 14]. The mechanism of the conversion of benzyl halides into arylacetic acids using iron pentacarbonyl is not as well defined as it is for reactions promoted by nickel or molybdenum carbonyl complexes. Iron



Scheme 8.4

pentacarbonyl is probably converted into the iron tetracarbonyl dianion and produces an acyliron ion pair $[\text{PhCH}_2\text{COFe}(\text{CO})_4\text{Q}^+]$. In mildly basic media, the interfacial base-catalysed cleavage of the complex anion is faster than the internal collapse of the ion to form a symmetrical ketone [11, 13, 14] (see Section 8.4). Consequently, the phase-transfer catalysed reaction leads to the predominant formation of the arylacetic acid with only low yields of the ketone. However, reaction of the acyliron species with reactive halides leads to the formation of the ketones (see Section 8.4) via the neutral complex $\text{PhCH}_2\text{COFe}(\text{R})(\text{CO})_4$. With stronger bases, the reaction is less selective [13].

In spite of the general lack of detailed understanding of mechanism, the procedure is superior to that using the cobalt catalyst both in the overall yields and in the specificity of the reaction to produce only mono-carbonylation products. Prolonged reaction times may lead, however, to the formation of benzyl esters of the acids, as a result of a catalysed reaction of the halide with the carboxylate anion.

When sodium ethoxide is used in place of sodium hydroxide in the carbonylation reaction of benzyl halides with dicobalt octacarbonyl, ethyl esters are produced instead of the acids [15]. Esters are also produced directly from iodoalkanes through their reaction with molybdenum hexacarbonyl in the presence of tetra-*n*-butylammonium fluoride [16]. Di-iodoalkanes produce lactones [16]. The reaction can be made catalytic in the hexacarbonyl by the addition of methyl formate [16]. *t*-Butyl arylacetic esters are produced in moderate yield (40–60%) under phase-transfer catalytic conditions in the palladium promoted carbonylation reaction with benzyl chlorides [17].

8.2.2 Preparation of arylacetic acids using a cobalt carbonyl complex

Method A: The benzyl halide (0.13 mol) is added slowly with stirring at 55°C over 1 h to $\text{NaCo}(\text{CO})_4$ (0.5 g, 2.6 mmol) and TEBA-Cl or TBA-Cl (4 mmol) in aqueous NaOH (40%, 50 ml) and Ph_2O (50 ml) under CO (1 atmos.). Stirring is continued for a further 2 h at 55°C and the aqueous phase is then separated, washed with Et_2O (2×25 ml) and acidified. The acidified aqueous phase is extracted with CH_2Cl_2 (3×25 ml) and the extracts washed with H_2O (25 ml), dried (MgSO_4), and evaporated to produce the arylacetic acid.

Method B: $\text{Co}_2(\text{CO})_8$ (0.17 g, 0.5 mmol) and TEBA-Cl (0.23 g, 1.0 mmol) in aqueous NaOH (5M, 25 ml) and PhH (25 ml) are stirred at room temperature for 30 min under CO (1 atmos.). The benzyl halide (25 mmol) is added and the reaction mixture is stirred at room temperature for *ca.* 12 h. The aqueous phase is separated, washed with PhH (2×25 ml) and acidified to produce the arylacetic acid (with arylpyruvic acid), which is isolated using the procedure described in 8.2.2.A. The PhH solutions contain the neutral products which are formed.

Method C: The benzyl halide (40 mmol) is added with stirring over 3 h under CO (1 atmos.) at 35°C to $\text{Co}_2(\text{CO})_8$ (0.34 g, 1.0 mmol) and TEBA-Br (1.0 g, 3.0 mmol) in *n*-butanol (25 ml) and aqueous KOH (50%, 25 ml). Stirring is continued until the uptake of CO ceases. The reaction mixture is acidified and the arylacetic acid isolated as described in 8.2.2.A. No dicarbonylation products are formed.

Method D: $\text{Co}(\text{Ph}_3\text{P})_2\text{Cl}_2$ (0.82 g, 1.25 mmol) and TBA-Br (0.32 g, 1 mmol) in aqueous NaOH (50%, 0.2 ml) and PhH (20 ml) are stirred under CO (1 atmos.) at room temperature for 3–4 h. The mixture is then stirred at 55°C and ArCH_2Cl (25 mmol) in PhH (10 ml) is added dropwise over 2.5 h. After further stirring for 8 h, the mixture is acidified with aqueous HCl and extracted with Et_2O (3×10 ml). The dried (MgSO_4) extracts are evaporated to yield the acid.

8.2.3 Carbonylation of alkyl halides to yield esters and lactones (Table 8.5)

Method A: The haloalkane (10 mmol) in PhH (20 ml) is added over 3 h at 25°C to $\text{Co}_2(\text{CO})_8$ (0.2 g, 0.6 mmol), NaOEt (1.7 g), and TBA-I (0.44 g, 1.2 mmol) under an atmosphere of CO. The reaction is monitored by TLC analysis and, when complete, the mixture is filtered. The solid is extracted with Et_2O (3×25 ml) and the organic solutions are fractionally distilled to give the ethyl ester.

Method B: NaBH_4 (53 mg, 1.4 mmol) is added to $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (0.29 g, 1.2 mmol) in THF (15 ml) under an atmosphere of CO. NaOEt (3.4 g) and TBA-I (0.44 g, 1.2 mmol) are added to the green solution and the mixture is stirred for 5 h. The haloalkane (20 mmol) in THF (30 ml) is added over 3 h and the ethyl ester is isolated as described in 8.2.3.A.

Method C: TBA- $\text{F}_3\text{H}_2\text{O}$ (6.31 g, 20 mmol), $\text{Mo}(\text{CO})_6$ (2.64 g, 10 mmol) and the iodoalkane (10 mmol) in THF (50 ml) are refluxed for 20 h. The mixture is cooled and poured into aqueous FeCl_3 (sat. soln, 50 ml) and extracted with $n\text{-C}_5\text{H}_{12}$ (3×25 ml). The organic solutions are combined and fractionally distilled to yield the ester (e.g. $n\text{-C}_8\text{H}_{17}\text{I}$ gave $\text{C}_8\text{H}_{17}\text{CO}_2\text{C}_8\text{H}_{17}$, 91%). Using the α,ω -di-iodoalkane (10 mmol), $\text{Mo}(\text{CO})_6$ (5.28 g, 20 mmol), TBA- $\text{F}_3\text{H}_2\text{O}$ (12.62 g, 40 mmol) in THF (100 ml) under similar conditions gave the lactone, which could be isolated from the reaction mixture by extraction with Et_2O (100 ml) [e.g. $\text{I}(\text{CH}_2)_4\text{I}$ gives δ -valerolactone, 69%; $\text{I}(\text{CH}_2)_5\text{I}$ gives ϵ -caprolactone, 67%; 2- $\text{Br}(\text{CH}_2)_2\text{C}_6\text{H}_4\text{CH}_2\text{Br}$ gives benzo- ϵ -caprolactone, 50%].

Method D: HCO_2Me (1.5 g, 25 mmol) is added to the iodoalkane (5 mmol), $\text{Mo}(\text{CO})_6$ (0.13 g, 0.5 mmol) and TBA- $\text{F}_3\text{H}_2\text{O}$ (3.15 g, 10 mmol) in THF (30 ml). The mixture is allowed to stand for 2 days at 40°C and then 2 days at 60°C and the ester is isolated as described in 8.2.3.C.

TABLE 8.5

Selected examples of the conversion of alkyl halides into ethyl esters using cobalt carbonyl complexes

RCH ₂ X		Product	% yield
R = Ph	X = Cl	$\text{PhCH}_2\text{CO}_2\text{Et}$	95
Ph	Br	$\text{PhCH}_2\text{CO}_2\text{Et}$	95
2-MeC ₆ H ₄	Cl	2-MeC ₆ H ₄ CH ₂ CO ₂ Et	80
4-MeOC ₆ H ₄	Cl	4-MeOC ₆ H ₄ CH ₂ CO ₂ Et	95
4-NO ₂ C ₆ H ₄	Cl	4-NO ₂ C ₆ H ₄ CH ₂ CO ₂ Et	20
2-ClC ₆ H ₄	Cl	2-ClC ₆ H ₄ CH ₂ CO ₂ Et	95
CH ₂ =CH	Cl	$\text{CH}_2=\text{CHCH}_2\text{CO}_2\text{Et}$	42
		$\text{MeCH}=\text{CHCO}_2\text{Et}$	40
CO ₂ Et	Cl	$\text{CH}_2(\text{CO}_2\text{Et})_2$	95
CO ₂ Et	Br	$\text{CH}_2(\text{CO}_2\text{Et})_2$	94
COPh	Cl	$\text{PhCOCH}_2\text{CO}_2\text{Et}$	20

Method E: CO is bubbled through *t*-BuOH (30 ml) and Pd(Ph₃P)₂Cl₂ (70 mg, 0.1 mmol), Ph₃P (0.13 g, 0.5 mmol), AcONa (0.9 g) and TEBA-Cl (0.23 g, 1 mmol) are added sequentially. The solution is stirred at 60–70°C for 1 h and the benzyl chloride, or phenacyl chloride (10 mmol) is then added. The mixture is refluxed for 20–24 h and then evaporated under reduced pressure. The residue is triturated with Et₂O (50 ml) and the ethereal solution is fractionally distilled to yield the *t*-butyl ester, RCO₂*t*-Bu (e.g. R = PhCH₂, 60%; 4-MeOC₆H₄CH₂, 45%; 4-O₂NC₆H₄CH₂, 42%; PhCOCH₂, 50%).

8.2.4 Preparation of arylacetic acids using an iron carbonyl complex (Table 8.6)

Fe(CO)₅ (50 mg, 0.25 mmol) is added with stirring to the benzyl halide (0.5 mmol) and TBA-HSO₄ (0.17 g, 0.5 mmol) in aqueous NaOH (1M, 10 ml) and CH₂Cl₂ (10 ml) under CO (1 atmos.). The mixture is stirred for *ca.* 24 h at 25°C and the organic phase is then separated, washed with H₂O (25 ml), dried (MgSO₄), and evaporated to give the neutral products. Acidification of the aqueous phase and extraction with CH₂Cl₂ gives the arylacetic acid.

TABLE 8.6

Selected examples of the conversion of benzyl halides into arylacetic acids using iron carbonyl complexes

ArCH ₂ X	% yield ArCH ₂ CO ₂ H	% yield of by-products	
		ArCH ₂ CO ₂ CO ₂ H	(ArCH ₂) ₂ and ArMe
PhCH ₂ Br	75	14	8
PhCH ₂ Cl	61	4	7
3-MeC ₆ H ₄ CH ₂ Br	54	27	5
3-MeC ₆ H ₄ CH ₂ Cl	31	8	0
2-MeC ₆ H ₄ CH ₂ Cl	69	7	10
2,4,6-Me ₃ C ₆ H ₂ CH ₂ Cl	37	5	0
3-MeOC ₆ H ₄ CH ₂ Cl	35	0	0
4-BrC ₆ H ₄ CH ₂ Br	50	9	7
3-CNC ₆ H ₄ CH ₂ Br	43	0 ^a	0
2-naphthylCH ₂ Br	55	0	0

^a 3% 3-HOCOC₆H₄CH₂COOH isolated.

The phase-transfer catalysed reaction of nickel tetracarbonyl with sodium hydroxide under carbon monoxide produces the nickel carbonyl dianions, Ni₅(CO)₁₅²⁻ and Ni₆(CO)₁₆²⁻, which convert allyl chloride into a mixture of but-3-enoic and but-2-enoic acids [18]. However, in view of the high toxicity of the volatile nickel tetracarbonyl, the use of the nickel cyanide as a precursor for the carbonyl complexes is preferred. Pretreatment of the cyanide with carbon monoxide under basic conditions is thought to produce the tricarbonylnickel cyanide anion [19], as the active metal catalyst. Reaction with allyl halides, in a manner analogous to that outlined for the preparation of the arylacetic acids, produces the butenoic acids (Table 8.7).

TABLE 8.7
Carboxylation of allyl halides

Allyl halide	% overall yield	% ratio of products	
		Unrearranged acid (But-3-enoic acid)	Rearranged acid (But-2-enoic acid)
$\text{CH}_2=\text{CHCH}_2\text{Br}$	98	21	79
$\text{CH}_2=\text{CHCH}_2\text{Cl}$	88	14	86
<i>E</i> -PhCH=CHCH ₂ Br	67	100	0
<i>E</i> -PhCH=CHCH ₂ Cl	84	100	0
<i>E</i> -MeCH=CHCH ₂ Br	91	44	4
		(Pent-3-enoic acid)	(2-Methylbut-3-enoic acid)
			52
			(Z-2-Methylbut-2-enoic acid)
$\text{Me}_2\text{C}=\text{CH}_2\text{Br}$	87	83	17
		(4-Methylpent-3-enoic acid)	(2,2-Dimethylbut-3-enoic acid)
$\text{CH}_2=\text{CHCH}(\text{Me})\text{Cl}$	93	14	68
		(2-Methylbut-3-enoic acid)	(Pent-3-enoic acid)
			18
			(Z-2-Methylbut-2-enoic acid)

8.2.5 Preparation of α,β - and β,γ -unsaturated carboxylic acids using a nickel carbonyl complex

The nickel carbonyl catalyst is preformed by passing a fast stream of CO through a two-phase system of aqueous NaOH (5M, 25 ml) and $\text{Me}_2\text{CHCH}_2\text{COMe}$ (25 ml) containing TBA- HSO_4 (0.07 g, 0.2 mmol). $\text{Ni}(\text{CN})_2$ (0.11 g, 1.0 mmol) is added and the mixture heated at 60°C for 3 h under CO (1 atmos.). The system is cooled to room temperature and the allyl halide (11.6 mmol) in $\text{Me}_2\text{CHCH}_2\text{COMe}$ (20 ml) is added over 3 h and the mixture is then stirred under CO (1 atmos.) for 12 h. The aqueous layer is separated, washed with Et_2O (2 × 25 ml) and acidified with sulphuric acid (3M). **CAUTION.** *HCN may be evolved.* The acidified solution is extracted with Et_2O (4 × 25 ml), and the extracts are washed with H_2O (20 ml), dried (MgSO_4) and evaporated to produce the acid.

Isomerism of the but-3-enoic acids into the *E*-but-2-enoic acids is base-catalysed (Table 8.8), whereas the formation of the other isomers indicates the participation of π -allylnickel complexes in the reaction. Potassium nickel tetracarbonyl is a considerably poorer catalyst, compared with nickel cyanide, whereas nickel sulphate and nickel iodide are ineffective catalysts.

Although the acylcobalt tetracarbonyls react with hydroxide ion under phase-transfer conditions, in the presence of alkenes and alkynes they form σ -adducts rapidly via an initial interaction with the π -electron system. Subsequent extrusion of the organometallic group as the cobalt tetracarbonyl anion leads to α,β -unsaturated ketones (see Section 8.4). In contrast, the cobalt carbonyl catalysed reaction of phenylethyne in the presence of iodomethane forms the hydroxybut-2-enolide (**5**) in

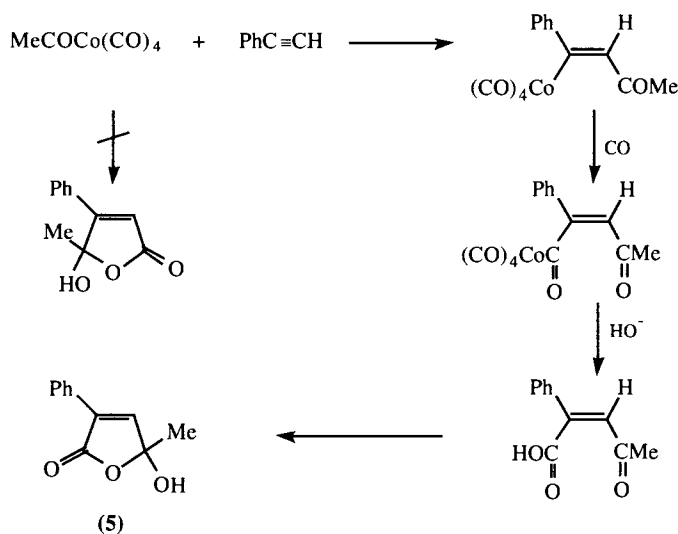
TABLE 8.8

Effect of hydroxide ion concentration upon the but-3- and but-2-enoic acid isomer ratios

Conc. of aq. NaOH	% overall yield ^a	% isomer ratio	
		But-3-enoic acid	<i>E</i> -But-2-enoic acid
0.5 M	25	100	0
1.0 M	59	100	0
1.5 M	86	93	7
5.0 M	98	21	79

^a Using 8.2.5.

a regiospecific manner (Scheme 8.5) [20, 21]. Cyclohexylethyne and 17-ethynyl-testosterone have also been reported to produce butenolides under similar conditions. The corresponding reaction using benzyl bromide in place of iodomethane produces only phenylacetic acid, indicating the greater instability of the phenacyl complex, compared with the acetyl derivative, under the basic liquid:liquid two-phase conditions. This problem is obviated by using solid:liquid phase-transfer catalysis [22].

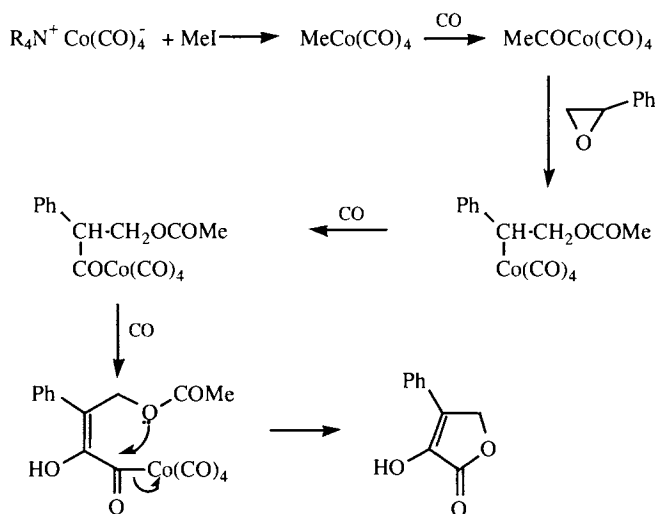


Scheme 8.5

8.2.6 Synthesis of butenolides

$\text{Co}_2(\text{CO})_8$ (35 mg, 0.1 mmol) in PhH (20 ml) is added to CTMA-Br (50 mg, 0.15 mmol) in aqueous NaOH (5M, 30 ml) and the mixture is stirred under CO (1 atmos.) for 2 h. Excess MeI (0.7 g, 5 mmol) is added, followed by $\text{PhC}\equiv\text{CH}$ (0.12 g, 1.2 mmol) and the reaction mixture is stirred until all of the ethyne is consumed. The organic phase is separated, washed with H_2O (3×20 ml), dried (Na_2SO_4), and evaporated to give the hydroxybutenolide, which is purified by chromatography from silica.

Isomeric hydroxylactones (furan-2,3-diones) result from the reaction of oxiranes with acetylcobalt tetracarbonyl. The initial σ -adduct undergoes further double carbonylation, via the enolic tautomer, and subsequent nucleophilic ring closure with the loss of the acetyl group (Scheme 8.6) [23]. An analogous reaction with vinyl-oxiranes leads to ring-opening of the oxirane ring to form β -hydroxycarboxylic acids, with no reaction involving the alkene group [24].

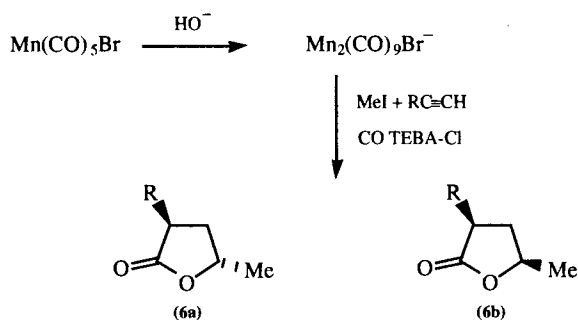


Scheme 8.6

8.2.7 Synthesis of the enol forms of 4,5-dihydro-4-phenylfuran-2,3-diones

The styrene oxide (26 mmol) is added with stirring to acetylcobalt tetracarbonyl, obtained at room temperature by the addition of an excess of MeI (9.0 g, 64 mmol) to CTMA-Br (0.2 g, 0.55 mmol) and $\text{Co}_2(\text{CO})_8$ (0.19 g, 0.55 mmol) under CO (1 atmos.). The mixture is stirred at room temperature for 12 h and the products are isolated using a work-up procedure analogous to that described in 8.2.6.

In contrast with the formation of the hydroxybutenolides, catalysed by cobalt carbonyls, the corresponding base-catalysed reaction of alkynes with manganese carbonyl complexes and iodomethane produces γ -lactones [25]. Although the mechanism is not clear, it is assumed that bromomanganese pentacarbonyl (or dimanganese decacarbonyl) reacts with the hydroxide ions to produce the dimanganese nonacarbonyl species [26, 27], which produces an intermediate acylmanganese complex, MeCOMn(CO)_4 in a manner analogous to the cobalt complex. Subsequent reaction with the alkyne leads to the isomeric γ -butyrolactones (**6a**) and (**6b**) (Scheme 8.7).



8.2.8 Carbonylation of alkynes to give 2-substituted 4-methyl- γ -butyrolactones (Table 8.9)

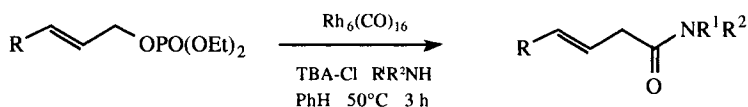
Aqueous NaOH (5M, 35 ml) and TEBA-Cl (0.1 g, 0.5 mmol) is added to $\text{Mn(CO)}_5\text{Br}$ (0.55 g, 2.0 mmol) in CH_2Cl_2 (35 ml) and the mixture is stirred at 35–40°C for 3 h under N_2 . The N_2 atmosphere is then replaced with CO. MeI (0.71 g, 5 mmol) in CH_2Cl_2 (2 ml) is added and the mixture is stirred at room temperature for 15 min. The alkyne (2 mmol) in CH_2Cl_2 (2 ml) is added and stirring is continued for a further 36 h at 35°C. The aqueous phase is then separated, washed with Et_2O (3×15 ml), neutralized to pH 7 with HCl, and extracted with Et_2O (3×20 ml). The ethereal extracts are dried (MgSO_4) and evaporated under reduced pressure to give the lactone, which can be purified by chromatography from silica.

The simple procedure for the carbonylation of allyl halides has been extended in the high yielding solid-liquid two-phase conversion of allyl phosphates into amides (60–80%) under the influence of a rhodium carbonyl cluster in the presence of primary or secondary amines (Scheme 8.8). A secondary product of the reaction is the allylamine, the concentration of which increases as the pressure of the carbon monoxide is reduced, such that it is the sole product (*ca.* 80%) in the absence of carbon monoxide [28].

TABLE 8.9
Synthesis of 2-substituted 4-methyl- γ -butyrolactones

Alkyne	Catalyst	Overall % yield of isomeric γ -lactones (6a and 6b)
$\text{PhC}\equiv\text{CH}$	$\text{Mn(CO)}_5\text{Br}$	75 ^a
	$\text{Mn}_2(\text{CO})_{10}$	65
$\text{Ph(CH}_2)_2\text{C}\equiv\text{CH}$	$\text{Mn(CO)}_5\text{Br}$	36
$n\text{-C}_4\text{H}_9\text{C}\equiv\text{CH}$	$\text{Mn(CO)}_5\text{Br}$	35
$n\text{-C}_6\text{H}_{13}\text{C}\equiv\text{CH}$	$\text{Mn(CO)}_5\text{Br}$	44
	$\text{Mn}_2(\text{CO})_{10}$	56
$4\text{-MeC}_6\text{H}_4\text{C}\equiv\text{CH}$	$\text{Mn(CO)}_5\text{Br}$	75

^a 47% *trans* isomer + 31% *cis* isomer. In the absence of a phase-transfer catalyst, 17% overall yield with a 7.5 : 1 *trans*:*cis* ratio.



Scheme 8.8

The reaction of but-1-en-3-yl diethyl phosphate with diethylamine produces *N,N*-diethylpent-3-enamide (86%), indicating that a π -allyl complex is involved in the carbonylation reaction. No isomerism to the α,β -unsaturated amides was observed.

8.2.9 Conversion of allyl phosphates into β,γ -unsaturated amides (Table 8.10)

The allyl phosphate (1.0 mmol), the amine (2.0 mmol), $\text{Rh}_6(\text{CO})_{16}$ (11 mg, 0.01 mmol), and TBA-Cl (28 mg, 0.1 mmol) in PhH (2 ml) are placed in an autoclave (10 ml), which is pressurized to 20 atmos. with CO. The autoclave is heated to 50°C and the mixture stirred for 3 h and then cooled to room temperature. Et_2O (25 ml) is added and the solution is washed with aqueous HCl (1M, 2×25 ml) to remove excess amine. The organic phase is dried (MgSO_4) and evaporated to give the amide.

TABLE 8.10
Carbonylation of allyl phosphates in the presence of amines

$\text{ROPO}(\text{OEt})_2$	Amine	% yield of β,γ -unsaturated amides
R = $\text{CH}_2=\text{CHCH}_2$	Et_2NH	86
	$\text{CH}_2=\text{CHCH}_2\text{NH}_2$	62
	Morpholine	74
<i>trans</i> $\text{MeCH}=\text{CHCH}_2$	1,2,3,4-Tetrahydroisoquinoline	84
<i>trans</i> $n\text{-PrCH}=\text{CHCH}_2$	Et_2NH	81
	Piperidine	82
	PhCH_2NH_2	80
<i>trans</i> $\text{PhCH}=\text{CHCH}_2$	Et_2NH	77

Lactones and lactams have also be prepared by the carbonylation of 2-(ω -hydroxyalkyl)- and 2-(ω -aminoalkyl)bromobenzenes [29] (see Section 8.3).

Partial hydration of nitriles to form amides is accomplished under mildly basic conditions, when catalysed by the addition of manganese pentacarbonyl bromide and benzyltriethylammonium chloride [30]. Yields are considerably reduced in the absence of the ammonium salt.

8.2.10 Conversion of nitriles into amides

Aqueous NaOH (5M, 35 ml) and TEBA-Cl (0.16 g, 0.7 mmol) are added to $\text{Mn}(\text{CO})_5\text{Br}$ (0.55 g, 2 mmol) in CH_2Cl_2 (35 ml) and the mixture is stirred at 40°C for 3 h. The nitrile (2 mmol) in CH_2Cl_2 (2 ml) is added and stirring is continued for a further 32 h at 40°C .

The aqueous phase is separated, washed with CH_2Cl_2 (3×15 ml), neutralized with aqueous HCl (1M), and extracted with Et_2O (3×20 ml). The ethereal extracts are dried (MgSO_4) and evaporated to yield the amide.

A cobalt catalysed carbonylation reaction converts *N*-substituted 1-aza-1,3-dienes into *N*-allylacetamides by a reductive acylation process [31]. Acetamides are by-products of the reaction. In contrast, Schiff bases undergo a double *N,C*-acetylation under the same conditions producing α -acetamido ketones and *N,N*-disubstituted acetamides [32].

8.2.11 Acetylation of *N*-substituted 1-aza-1,3-dienes

A fast stream of CO is bubbled through TEBA-Cl (0.14 g, 0.5 mmol) degassed in PhH (20 ml) and H_2O (20 ml). $\text{Co}_2(\text{CO})_8$ (0.68 g, 2 mmol) and MeI (2.35 g) are added, followed by the azadiene (2 mmol), and the mixture is stirred at room temperature until the solution is bright red. The aqueous phase is separated, extracted with CH_2Cl_2 (5×25 ml), and the combined organic solutions are dried (MgSO_4) and evaporated. The allylacetamide and acetamide are separated by chromatography from silica [e.g. $\text{PhCH}=\text{CHCH}_2\text{N}(\text{ToI})\text{COMe}$, 65%, ToINHCOMe , 50% from $\text{ToI}\text{N}=\text{CHCH}=\text{CHPh}$; $\text{PhCH}=\text{C}(\text{Me})\text{CH}_2\text{N}(\text{ToI})\text{COMe}$, 41%, ToINHCOMe , 32% from $\text{ToI}\text{N}=\text{CHC}(\text{Me})\text{C}=\text{CHPh}$; $\text{PhCH}=\text{CHCH}_2\text{N}(4\text{-MeOC}_6\text{H}_4)\text{COMe}$, 50%, $4\text{-MeOC}_6\text{H}_4\text{NHCOMe}$, 33% from $4\text{-MeOC}_6\text{H}_4\text{N}=\text{CHCH}=\text{CHPh}$].

8.2.12 Double acetylation of Schiff bases

A stream of CO is bubbled through TEBA-Cl (0.14 g, 0.5 mmol) in degassed PhH (40 ml) and aqueous NaOH (0.33 M, 20 ml). $\text{Co}_2(\text{CO})_8$ (0.68 g, 2 mmol) and MeI (4.7 g) are added and the mixture is stirred for 5 min at room temperature. The Schiff base (1.5 mmol) is added and the mixture is heated to 60°C for ca. 3 h. The product is isolated as described in 8.2.11 [e.g. $\text{PhCH}(\text{COMe})\text{N}(\text{Ph})\text{COMe}$ (50%) and $\text{PhCH}_2\text{N}(\text{Ph})\text{COMe}$ (2%) from $\text{PhCH}=\text{NPh}$; $\text{PhCH}(\text{COMe})\text{N}(\text{Me})\text{COMe}$ (40%) and PhCHO (30%) from $\text{PhCH}=\text{NMe}$].

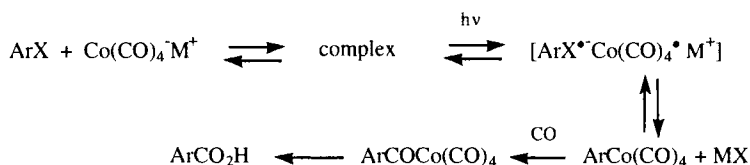
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8.3 CARBONYLATION OF ARYL AND VINYL HALIDES LEADING TO CARBOXYLIC ACIDS AND RELATED COMPOUNDS

Direct nucleophilic displacement of halide ions from haloarenes is feasible under mild conditions only when the reaction is aided by the presence of mesomeric electron-withdrawing substituents at positions *ortho* and/or *para* to the halogen (see Chapter 2). Conditions can be established, however, for an $S_{RN}1$ reaction using a cobalt carbonyl catalyst [1, 2]. Under conditions analogous to those described in Section 8.2, a homogeneous solution of the haloarene and the quaternary ammonium cobalt tetracarbonyl is obtained which, upon irradiation at 350 nm, undergoes an $S_{RN}1$ reaction to produce the arylcobalt tetracarbonyl (Scheme 8.9). Subsequent carbonylation and base-catalysed cleavage of the complex yields the benzoic acid. The reaction is selective in that, although bromobenzene can be converted into benzoic acid in high yield (95%), chlorobenzene is unreactive (Table 8.11). In many respects, the procedure is therefore superior to the normal Grignard conversion of haloarenes into benzoic acids.



Scheme 8.9

TABLE 8.11
S_{NR}¹ carbonylation of haloarenes

Haloarene	Reaction time at 65 °C	Product	% yield
PhCl	13 h	No reaction	–
PhBr	1.5 h	PhCO ₂ H	97
PhI	1 h	PhCO ₂ H	90
4-MeC ₆ H ₄ Br	1.5 h	4-MeC ₆ H ₄ CO ₂ H	97
2-MeC ₆ H ₄ Br	2.25 h	2-MeC ₆ H ₄ CO ₂ H	96
4-MeOC ₆ H ₄ Br	2 h	4-MeOC ₆ H ₄ CO ₂ H	98
2-MeOC ₆ H ₄ Br	2 h	2-MeOC ₆ H ₄ CO ₂ H	50 ^a
4-FC ₆ H ₄ Br	2 h	4-FC ₆ H ₄ CO ₂ H	97
4-ClC ₆ H ₄ Br	1 h	4-ClC ₆ H ₄ CO ₂ H	98
4-AcC ₆ H ₄ Br	4.5 h	4-AcC ₆ H ₄ CO ₂ H	90
4-BrC ₆ H ₄ CO ₂ Et	1.5 h	1,4-C ₆ H ₄ (CO ₂ H) ₂	97
1-Br naphthalene	5 h	1-Naphthoic acid	95
2-Br-naphthalene	5 h	2-Naphthoic acid	97

^a + 47% anisole.

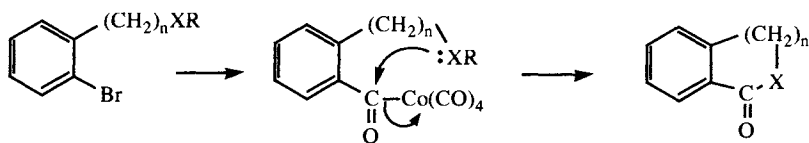
It is noteworthy that, although 4-bromoanisole produces anisic acid in high yield, 4-hydroxybenzoic acid is isolated in only 17% yield from the corresponding reaction of 4-bromophenol. Also, 4-bromoacetophenone, which may react by a normal S_N reaction, is readily converted into 4-acetylbenzoic acid, whereas 4-bromonitrobenzene produces 4-nitrobenzoic acid in only 17% yield, together with nitrobenzene (17%).

8.3.1 Preparation of benzoic acids via the S_{NR}¹ reaction

A slow stream of CO is passed into a two-phase mixture of the bromoarene (20 mmol), Co₂(CO)₈ (0.35 g, 1.0 mmol) and TBA-Br (0.64 g, 2.0 mmol) in aqueous NaOH (5M, 50 ml) and PhH (25 ml) in a Pyrex flask. The mixture is irradiated using a Rayonet® (or similar) photochemical reactor (350 nm) and, on completion of the reaction, the aqueous phase is separated, washed with Et₂O (2 × 25 ml), and acidified to yield the benzoic acid.

The reaction has also been applied to the conversion of vinyl bromides into acrylic acids, e.g. 1-bromo- and 1-chlorocyclooctene are converted into cyclooctene-1-carboxylic acid (*ca.* 98%) [3], 2-chloro-3,3-dimethylbut-1-ene yields 4,4-dimethylpent-2-enoic acid (95%), and *trans*-cinnamic acid is obtained (85%) from *trans*-β-bromostyrene. *cis*-β-Bromostyrene produces a mixture of *cis*- and *trans*-cinnamic acids in 38 and 42% yields, respectively [3]. In these reactions, benzyltriethylammonium chloride cannot be used as the phase-transfer catalyst, as it leads to the production of phenylacetic acid [3].

By a procedure analogous to that used for the production of benzoic acids, it is possible to produce benzolactones and benzolactams (Scheme 8.10) in good yield (60–95%) from suitable 2-(hydroxyalkyl)- and 2-(aminoalkyl)bromobenzenes. The

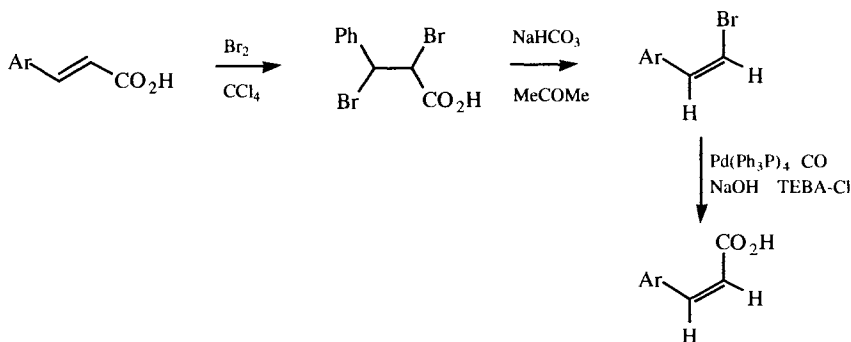


Scheme 8.10

reaction is promoted by cobalt carbonyl complexes, but a combination of cobalt nitrate and potassium cyanide can be used with equal effect.

In a slightly less convenient procedure, but one which has general versatility, carbonylation of aryl (or vinyl) palladium compounds produces aryl, heteroaryl, and vinyl carboxylic acids. As with the other procedures, immediate upon its formation, the carboxylate anion migrates to the aqueous phase. Consequently, haloaromatic acids can be obtained from dihaloarenes, without further reaction of the second halogen atom, e.g. 1,4-dibromobenzene has been carbonylated (90% conversion) to yield 4-bromobenzoic acid with a selectivity for the monocarbonylation product of 95%. Additionally, the process is economically attractive, as the organic phase containing the catalyst can be cycled with virtually no loss of activity and *ca.* 4000 moles of acid can be produced for each mole of the palladium complex used [4].

As the insertion of the carbon monoxide retains the configuration of the Pd-C bond, a modification of the procedure permits the conversion of *trans*-cinnamic acid into the *cis*-isomer (Scheme 8.11) [5].



Scheme 8.11

8.3.2 Preparation of benzoic acids using palladium complexes

The haloarene (0.4 mol) and Ph_3P (0.2 g) are added with stirring at 95°C over 4 h to $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ (0.18 g, 0.26 mmol) and TBA-I (0.6 g, 1.6 mmol) in a xylene (50 ml):aqueous NaOH (30%, 220 ml) two-phase system under CO (5 atmos). The mixture is stirred for a further hour and then the aqueous phase is separated, washed with Et_2O (2×25 ml), and acidified to produce the aromatic acid.

8.3.3 Conversion of *trans*-cinnamic acids into the *cis*-isomers (Table 8.12)

TEBA-Cl (0.12 g, 0.5 mmol) in aqueous NaOH (5M, 15 ml) is stirred under N_2 for 15 min. $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.14 g, 0.12 mmol) in CH_2Cl_2 (5 ml) and $\text{Me}_2\text{C}(\text{Et})\text{OH}$ (15 ml) is then

TABLE 8.12

Palladium-catalysed conversion of <i>cis</i> -bromostyrenes into <i>cis</i> -cinnamic acids		
<i>cis</i> -ArCH=CHBr	% yield	
	<i>cis</i> -Cinnamic acid	1,4-Diarylbuta-1,3-diene
Ar = Ph	56	Trace
4-ClC ₆ H ₄	47	16.7
3-BrC ₆ H ₄	35	17.1
4-MeC ₆ H ₄	49	8.4
4-CF ₃ C ₆ H ₄	48	21.4
2-MeC ₆ H ₄	54	—

added and the N₂ replaced with an atmosphere of CO. The *cis*- β -bromostyrene (2.75 mmol), obtained from the *trans*-cinnamic acid [5], in Me₂C(Et)OH (5 ml) is added and the mixture stirred under CO for 12 h. The aqueous phase is separated and extracted with Et₂O (2 \times 15 ml), and the organic phase is washed with H₂O (20 ml). The combined organic solutions are dried (MgSO₄) and evaporated to yield the *cis*-cinnamic acid, which is purified by chromatography from silica.

Aromatic acid chlorides are converted into the corresponding anhydrides in high yields (>95%), when reacted with carbon monoxide under solid:liquid basic catalysed conditions in the presence of a complexed cobalt or palladium salt [6]. In the absence of the quaternary ammonium salt, only hydrolysis to the carboxylic acid occurs.

8.3.4 Anhydrides from acid chlorides

The acid chloride (0.38 mol) and CO(Ph₃P)₂Cl₂ (6.55 g, 10 mmol) in MeCN (50 ml) are added to NaHCO₃ (32 g) and TBA-Br (3.2 g, 10 mmol) and the mixture is stirred at 120°C for *ca.* 12 h. The cooled reaction mixture is poured into H₂O (150 ml) and the precipitated product is washed well with aqueous NaOH (5%), aqueous HCl (5%) and H₂O [e.g. (PhCO)₂O, 94%; (4-MeC₆H₄CO)₂O, 96%; (4-O₂NC₆H₄CO)₂O, 90%; (PhCH=CHCO)₂O, 96%].

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8.4 CARBONYLATION REACTIONS LEADING TO KETONES AND ALDEHYDES

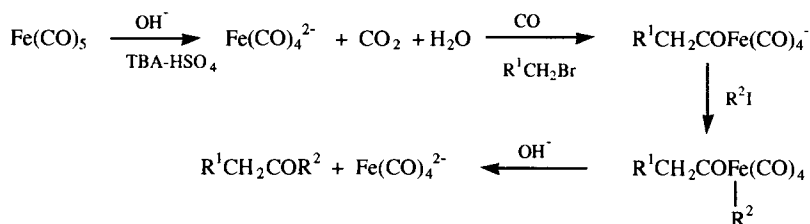
In contrast with the predominant conversion of haloalkanes into carboxylic acids by the iron carbonyl promoted reaction in the presence of dilute aqueous sodium hydroxide, the corresponding reaction with concentrated aqueous sodium hydroxide, or where the preformed dianion is used, leads to the preferential formation of ketones [1]. The remarkable differences in the reported effects of the base strength has led to the need for a strongly basic aqueous phase to be questioned. Equally, an atmosphere of carbon monoxide above the reaction system may not be critical, as it has been shown that the use of saturated aqueous calcium hydroxide under an atmosphere of nitrogen produces better selectivity for the formation of symmetrical ketones. The intermediate iron tetracarbonyl complex, RCOFe(R)(CO)_4 , decomposes preferentially to form the symmetrical ketone (Table 8.13) with a high yield of dibenzyl ketone from benzyl bromides, whereas benzyi chloride is virtually unreactive (*cf.* Section 8.3) and, without activation of the aryl ring to nucleophilic attack, all haloarenes are totally unreactive. Simple iodoalkanes produce symmetrical dialkyl ketones in good yields, whereas the corresponding chlorides and bromides, although they form the acyliron complexes, do not produce the acyl(alkyl)iron complexes. This lack of reactivity can be utilized in the synthesis of unsymmetrical ketones [1] by the reaction of the acyliron complexes with an alkyl iodide (Scheme 8.12) (Table 8.14). The validity of this work has been challenged [2], as it has been shown that, in the carbonylation of benzyl bromides under strongly basic conditions, arylacetic acids and esters are formed as well as the ketones; the ketones predominate when a weakly basic medium is used (8.4.1.B). Under analogous conditions, 1,2-bis(bromomethyl)benzene is converted into the *o*-quinodimethane-iron tricarbonyl complex [2].

TABLE 8.13
Selected examples of the synthesis of symmetrical ketones

Haloalkane	Reaction time	Product	% yield
PhCH_2Cl	13 h	$(\text{PhCH}_2)_2\text{CO}$	3
PhCH_2Br	3 h	$(\text{PhCH}_2)_2\text{CO}$	94
$4\text{-ClC}_6\text{H}_4\text{CH}_2\text{Cl}$	3 h	$(4\text{-ClC}_6\text{H}_4\text{CH}_2)_2\text{CO}$	88
$4\text{-MeC}_6\text{H}_4\text{CH}_2\text{Cl}$	3 h	$(4\text{-MeC}_6\text{H}_4\text{CH}_2)_2\text{CO}$	98
$n\text{-C}_8\text{H}_{17}\text{I}$	30 h	$(n\text{-C}_8\text{H}_{17})_2\text{CO}$	91
$n\text{-C}_8\text{H}_{17}\text{Br}$	30 h	$(n\text{-C}_8\text{H}_{17})_2\text{CO}$	Trace

TABLE 8.14
Selected examples of the synthesis of unsymmetrical ketones

Alkylating system	Reaction time	Product	% yield
$n\text{-C}_8\text{H}_{17}\text{Br}$ (+ EtI)	5 h	$n\text{-C}_8\text{H}_{17}\text{COEt}$	45
$n\text{C}_{16}\text{H}_{33}\text{Br}$ (+ EtI)	5 h	$n\text{-C}_{16}\text{H}_{33}\text{COEt}$	60
PhCOCl (+ EtI)	5 h	PhCOEt	15



Scheme 8.12

In a similar type of reaction, polymer-supported hydridoiron tetracarbonyl anion reacts with simple non-benzylic aliphatic bromides and iodides to produce aldehydes (Table 8.15), presumably through the intermediate formation of RCOFeH(CO)_3 , which undergoes reductive extrusion of the aldehydes [3]. In contrast, benzylic halides and α -halocarbonyl compounds are reductively dehalogenated by the HFe(CO)_4^- anion (see Chapter 11).

TABLE 8.15
Selected examples of the synthesis of aldehydes using
polymer-supported catalyst

Haloalkane	Aldehyde	% yield
<i>n</i> -C ₇ H ₁₅ Br	<i>n</i> -C ₇ H ₁₅ CHO	90
<i>n</i> -C ₈ H ₁₇ Br	<i>n</i> -C ₈ H ₁₇ CHO	90 ^a
<i>n</i> -C ₈ H ₁₇ I	<i>n</i> -C ₈ H ₁₇ CHO	95
PhCH ₂ CH ₂ Br	PhCH ₂ CH ₂ CHO	80
Br(CH ₂) ₃ CO ₂ Et	OHC(CH ₂) ₃ CO ₂ Et	85

^a 60% yield, when *n*-C₆H₁₄ used as solvent under reflux for 10 hours.

8.4.1 Preparation of symmetrical aliphatic ketones

Method A: The bromoalkane (1.5 mmol), Fe(CO)_5 (0.29 g, 1.5 mmol), and TBA-Br (60 mg, 0.18 mmol) are added to aqueous NaOH (33%, 4 ml) and PhH (4 ml) and the mixture is stirred for *ca.* 3 h under N₂. The reaction mixture is then poured into a solution of iodine in PhH and stirred for 30 min. The PhH solution is separated and washed with aqueous Na₂S₂O₃ (10%), dilute HCl (10%, 2 × 10 ml) and H₂O (10 ml), dried (Na₂SO₄), and evaporated to produce the symmetrical ketone.

Method B: A thermostatted vessel (20°C) is purged several times with N₂. Ca(OH)_2 (0.3 g, 4 mmol) and TBA-HSO₄ (0.17 g, 0.5 mmol) are introduced into the apparatus, followed by degassed H₂O (10 ml) and CH₂Cl₂ (10 ml). The benzyl halide (2 mmol) and Fe(CO)_5 (0.19 g, 1 mmol) are then added with stirring (1200 r.p.m.) and the mixture is stirred until all of the halide is consumed. Air is then bubbled through the reaction mixture to destroy iron carbonyl residues. The symmetrical ketones, together with any neutral by-products, are isolated from the organic phase. Acidification of the aqueous phase yields arylacetic acids.

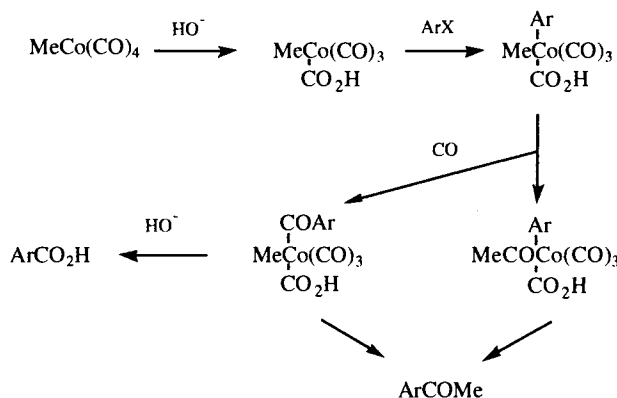
8.4.2 Preparation of unsymmetrical aliphatic ketones

Using a procedure analogous to 8.4.1.A, the benzyl halide is replaced by a simple bromo- or chloroalkane (1.5 mmol) and the two-phase system is stirred at room temperature for 12 h. The reactive iodoalkane (4.5 mmol) is then added and the reaction mixture is stirred for a further 5 h. The unsymmetrical ketone is isolated as described in 8.4.1.A.

8.4.3 Polymer-supported preparation of aliphatic aldehydes

The polymer-supported hydridoiron tetracarbonyl (33 mmol) is prepared by the addition of $\text{Fe}(\text{CO})_5$ (6.46 g, 33 mmol) to KOH (5.6 g, 0.1 mol) in aqueous EtOH (1:1 v/v, 100 ml) under N_2 . The mixture is heated with stirring under reflux for 2 h and Amberlyst A-26 resin (24 g) is then added and the mixture is stirred for a further 15 min. The resin is collected, washed with degassed H_2O (to neutrality), MeOH and Et_2O , dried at room temperature under a flow of N_2 , and used immediately. The haloalkane (11 mmol) in THF (50 ml) is added to the resin and the mixture is stirred under reflux for *ca.* 4 h. When GLC analysis shows the reaction to be complete, the resin is removed by filtration, and the filtrate evaporated under reduced pressure to give the aliphatic aldehyde.

Aryl methyl ketones have been obtained [4, 5] by a modification of the cobalt-catalysed procedure for the synthesis of aryl carboxylic acids (8.3.1). The cobalt tetracarbonyl anion is converted initially by iodomethane into the methyltetracarbonyl cobalt complex, which reacts with the haloarene (Scheme 8.13). Carboxylic acids are generally obtained as by-products of the reaction and, in several cases, it is the carboxylic acid which predominates. Unlike the carbonylation of haloarenes to produce exclusively the carboxylic acids [6, 7], the reaction does not need photo-initiation. Replacement of the iodomethane with benzyl bromide leads to aryl benzyl ketones in low yield, e.g. 1-bromonaphthalene produces the benzyl ketone (15%), together with the 1-naphthoic acid (5%), phenylacetic acid (15%), 1,2-diphenylethane (15%), dibenzyl ketone (1%), and 56% unchanged starting material [4, 5]. α -Bromomethyl ketones 'dimerize' in the presence of cobalt octacarbonyl and



Scheme 8.13

benzyltriethylammonium chloride to produce 1,4-disubstituted butan-1,4-diones in variable yield, together with the debrominated methyl ketone [8].

8.4.4 Aryl methyl ketones via the cobalt-catalysed carbonylation of aryl halides (Table 8.16)

CTMA-Br (0.07 g, 0.2 mmol) in aqueous NaOH (1 M, 25 ml) is added to $\text{Co}_2(\text{CO})_8$ (0.07 g, 0.3 mmol) in PhH (15 ml) and the mixture is stirred at 20°C for 2 h. The aryl halide (1 mmol) and MeI (1.4 g, 10 mmol) in PhH (10 ml) are added and the mixture is stirred for a further 20 h. The organic phase is then separated, washed with H_2O (2×15 ml), dried (Na_2SO_4), and evaporated to yield the ketone, which is purified by chromatography from silica. Acidification of the aqueous phase produces the carboxylic acid.

TABLE 8.16
Selected examples of the synthesis of aryl methyl ketones

Haloarene	% yield	
	Aryl methyl ketone	Carboxylic acid
PhBr	4.0	14.9 ^{a,b}
4-BrC ₆ H ₄ Cl	19.2	10.0 ^{c,d}
4-BrC ₆ H ₄ C ₆ H ₅	34.0	22.9
1-Bromonaphthalene	54.0	20.0 ^{e,f}
3-Iodobenz[<i>b</i>]thiophene	13.0	30.0 ^g
3-Iododibenzfuran	34.6	14.4
3-Bromoquinoline	38.0	<i>h</i>
2-Chloroquinoline	15.0 ⁱ	<i>h</i>
6-Chloro-2-methyl-4-phenylpyrimidine	4.2 ^j	<i>h</i>
6-Iodo-2-methyl-4-phenylpyrimidine	27.0 ^k	<i>h</i>

^a 6% ketone and 57.8% acid, when the reaction is conducted at 60°C. ^b 69% of starting material recovered. ^c 46.9% ketone and 36.4% acid, when the reaction is conducted at 60°C. ^d 52% of starting material recovered. ^e +3% 1-formylnaphthalene and 2% di-(1-naphthyl) ketone. Use of $\text{Ca}(\text{OH})_2$ in place of NaOH leads the additional formation of 4-(1-naphthyl)pyruvic acid. ^f 21% of starting material recovered. ^g +45% benz[*b*]thiophene. ^h Acid fraction not examined. ⁱ +30% 2-methylquinoline. ^j +34% 2,6-dimethyl-4-phenyl-pyrimidine. ^k +54% 2,6-dimethyl-4-phenylpyrimidine.

Table 8.17 shows the scope of the reaction of acetylcobalt tetracarbonyl with polyenes. The reactions are regiospecific with the acetyl group adding to the terminal unsaturated carbon atom of the π -electron system to produce the *E*- α,β -unsaturated ketones [9]. In the reaction with fulvenes [10], only the 1-acetyl and 1,4-diacetyl derivatives are formed, with no evidence of the 2-isomer. This is an indication of the relative stabilities of the cyclic π -allyl complexes, compared with the exocyclic complex. It has been postulated that, in the reactions of conjugated systems, the initial σ -allyl adduct proceeds to the products via the π -allyl complex (*cf.* Scheme 8.1), whereas in the case of unconjugated π -systems, the initial σ -adduct is more stable and tends to undergo a further carbonylation reaction.

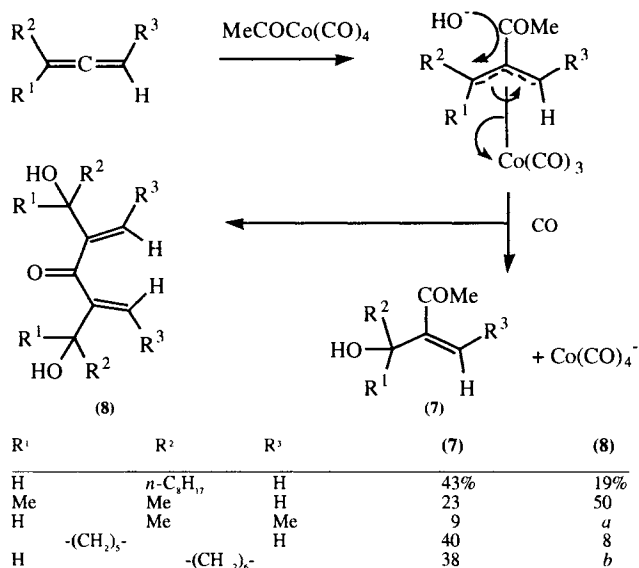
TABLE 8.17
Selected examples of the reactions of polyenes with $\text{MeCoCo}(\text{CO})_4$

Polyene	Acetyl product	% yield
$E\text{-Ph}(\text{CH}=\text{CH})_2\text{H}$	$E,E\text{-Ph}(\text{CH}=\text{CH})_2\text{COMe}$	86
$E,E\text{-Ph}(\text{CH}=\text{CH})_3\text{H}$	$E,E,E\text{-Ph}(\text{CH}=\text{CH})_3\text{COMe}$	43
$\text{CH}_2=\text{CHC}(\text{Me})=\text{CH}_2$	$\text{CH}_2=\text{C}(\text{Me})\text{CH}=\text{CHCOMe}$	42
$E,E\text{-Ph}(\text{CH}=\text{CH})_2\text{Ph}$	$E,Z\text{-PhCH}=\text{CH}\cdot\text{CH}=\text{C}(\text{Ph})\text{COMe}$	32
$\text{MeO}(\text{CH}=\text{CH})_2\text{H}$	$\text{MeO}(\text{CH}=\text{CH})_2\text{COMe}$	13
1-Vinylcyclohex-1-ene	1-(Cyclohex-1-en-1-yl)but-1-en-3-one	63
1-Fe(Cp)buta-1,3-diene ^a	3-Acetyl-1-Fe(Cp)buta-1,3-diene	82
Cyclohexa-1,3-diene	1-Acetylcyclohexa-1,3-diene	54
Fulvene	2-Acetylfulvene	74
6,6-Diarylfulvenes	2-Acetyl-6,6-diarylfulvenes	46–71

^a Cp = η -cyclopentadienyl derivative.

8.4.5 Acetylation of polyenes

$\text{Co}_2(\text{CO})_8$ (44 mg, 0.13 mmol) in PhH (20 ml) is added to TEBA-Cl (0.2 g, 0.88 mmol) in aqueous NaOH (5M, 20 ml) and the mixture is stirred at room temperature under CO (1 atmos.) for 1.5 h. MeI (0.7 g, 5 mmol) is added and, after the mixture has been stirred for a further 2 h, the polyene (1.5 mmol) is introduced. The reaction mixture is stirred for 2 h and the organic phase is then separated, washed with H_2O (3×20 ml), dried (Na_2SO_4), and evaporated to give the acetylpolyene, which is purified by chromatography from silica.



^a 14% 3,5-bis(ethylideno)-2,6-dimethyltetrahydropyr-4-one. ^b 15% 1-acetylcycloheptene.

Scheme 8.14

Acetylation occurs at the 2-position of allene systems (Scheme 8.14). The intermediate π -allyl complex breaks down via the nucleophilic displacement of the cobalt carbonyl group by the hydroxide ion to produce the hydroxyketone (7) [11]. An alternative oxygen-initiated radical decomposition of the complex cannot, however, be totally precluded. The formation of a second major product, the divinyl ketone (8), probably arises from direct interaction of the dicobalt octacarbonyl with the allene and does not require the basic conditions.

8.4.6 Hydroxyacetylation of allenes

$\text{Co}_2(\text{CO})_8$ (3.4 g, 10 mmol) and CTMA-Br (0.1 g, 0.27 mmol) are added to aqueous NaOH (5M, 20 ml) and PhH (20 ml) and the mixture is stirred for 3 h under CO (1 atmos.). MeI (11.5 g, 80 mmol) and the allene (10 mmol) are added and the mixture is stirred for a further 3 h under CO. Air is then introduced to decompose the metal carbonyl and the organic phase is separated, washed with H_2O (2×20 ml), dried (MgSO_4), and evaporated to give the hydroxyketone, which is purified further by chromatography from silica.

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Elimination Reactions, Cleavage and Rearrangement Reactions, Isomerism and H/D Exchange Reactions

9.1 ELIMINATION REACTIONS

The dehydrohalogenation of 1- or 2-haloalkanes, in particular of 1-bromo-2-phenylethane, has been studied in considerable detail [1–9]. Less active haloalkanes react only in the presence of specific quaternary ammonium salts and frequently require stoichiometric amounts of the catalyst, particularly when Triton B is used [1, 2]. Elimination follows zero order kinetics [7] and can take place in the absence of base, for example, styrene, equivalent in concentration to that of the added catalyst, is obtained when 1-bromo-2-phenylethane is heated at 100°C with tetra-*n*-butylammonium bromide [8]. The reaction is reversible and 1-bromo-1-phenylethane is detected at 145°C [8]. From this evidence it is postulated that the elimination follows a reverse transfer mechanism (see Chapter 1) [5]. The liquid:liquid two-phase β -elimination from 1-bromo-2-phenylethanes is low yielding and extremely slow, compared with the PEG-catalysed reaction [4]. In contrast, solid potassium hydroxide and tetra-*n*-butylammonium bromide in *t*-butanol effects a 73% conversion in 24 hours or, in the absence of a solvent, over 4 hours [3]; extended reaction times lead to polymerization of the resulting styrene.

A study of Hofmann vs Saytzeff elimination from 2-bromooctane under solid:liquid two-phase conditions [6] shows that the 1-octene:2-octene ratio depends not only on the base used, but also on the catalyst. Aliquat is the most effective catalyst giving a 98% overall yield with a 1-octene:2-octene ratio of *ca.* 2:1. Benzyltriethylammonium chloride catalyses a 95% conversion with a ratio of *ca.* 3:1 in favour of the 1-octene. Potassium hydroxide and potassium *t*-butoxide favour the formation of 1-octene, whereas sodium methoxide and sodium ethoxide favour the formation of 2-octene [6].

Alkynes have been prepared from 1,1- and 1,2-dihaloalkanes and from haloalkenes under the influence of a quaternary ammonium salt; *geminal*- and *vic*-dibromoalkanes are converted into alkynes under liquid:liquid [10, 11] and solid:liquid [12–14] conditions with Aliquat or tetra-*n*-octylammonium bromide

TABLE 9.1
Selected examples of alkynes from dibromoalkanes

Alkyne	Reaction conditions	% yield
$n\text{-C}_4\text{H}_9\text{C}\equiv\text{CH}$	9.1.2.A/90°C/6 h	92
$n\text{-C}_6\text{H}_{13}\text{C}\equiv\text{CH}$	9.1.2.A/90°C/6 h	88
$n\text{-C}_{14}\text{H}_{29}\text{C}\equiv\text{CH}$	9.1.2.A/90°C/6 h	88
$t\text{-BuC}\equiv\text{CH}$	9.1.2.A/90°C/6 h	86
$\text{HC}\equiv\text{CCH}(\text{OEt})_2$	9.1.2.A/80°C/6 h	79
	9.1.1.A/30 min	80
$\text{HC}\equiv\text{CCH}_2\text{OEt}^a$	9.1.2.A/90°C/8 h	47
$\text{ClC}\equiv\text{CCH}(\text{OEt})_2$	9.1.1/30 min	70 ^b
$\text{PhC}\equiv\text{CH}$	9.1.2.A/80°C/1 h	98
	9.1.1/30 min	87
4-MeC ₆ H ₄ C≡CH	9.1.2.A/35°C/8 h	96
	9.1.1/30 min	77 ^c
2-ThienylC≡CH ^d	9.1.2.A/90°C/8 h	58
PhC≡CPh	9.1.2.A/80°C/1 h	96
	9.1.1/30 min	75
4-ClC ₆ H ₄ C≡C(4-ClC ₆ H ₄)	9.1.2.A/20°C/8 h	84

^a From BrCH=CHOEt. ^b From Cl₂C=CHCH(OEt)₂. ^c from 4-MeC₆H₄CCl=CH₂. ^d From 1,1-dichloro-2-(2-thienyl)ethane.

(Table 9.1). The rate of dehydrobromination from the intermediate bromoalkenes follows the pattern 2-bromoalkenes > *Z*-1-bromoalkenes > *E*-1-bromoalkenes; the corresponding chloro derivatives react more slowly. For optimum yield, the reaction temperature should be <100°C to reduce decomposition of the catalyst, and the concentration of base should be kept low to prevent isomerization of the resulting alkynes. β-Elimination of HBr from 1,2-dibromo-1-phenylethane can be controlled to yield 1-bromo-1-phenylethene in 83% yield [15]. The addition of alcohols and diols have a co-catalytic effect on the elimination reaction, as the alkoxide anions are transferred more effectively than the hydroxide ions into the organic phase [13].

2,2-Dimethylbut-3-yne has been obtained under basic solid:liquid two-phase conditions in the presence of Aliquat from 1,1-dichloro-3,3-dimethylbutane [16]. 2-Methylbut-3-yne can be obtained under similar conditions, as can but-1-en-3-yne, by a double elimination from 1,4-dichlorobut-2-ene. In all cases, the addition of a catalytic amount of pinacol aids the reaction.

9.1.1 Liquid:liquid two-phase conversion of *vic*-dibromoalkanes into alkynes

The dibromo compound (10 mmol) and TBA-HSO₄ (10.2 g, 30 mmol) in *n*-C₅H₁₂ (20 ml) are stirred with aqueous NaOH (50%, 7 ml). After the ensuing exothermic reaction subsides, the mixture is refluxed for 30 min. The mixture is then washed with aqueous H₂SO₄ (25%, 12 ml) and the organic phase is separated, dried (Na₂SO₄), and evaporated to yield the alkyne.

9.1.2 Solid:liquid two-phase conversion of *vic*-dihaloalkanes into alkynes

Method A: The dihaloalkane (0.1 mol) and Aliquat (or TOA-Br) (1 mmol) in petroleum ether (100 ml; b.p. appropriate for separation from the alkyne by distillation) are added to powdered KOH (14 g, 0.25 mol) and the mixture is stirred for 1–8 h (Table 9.1). The mixture is then filtered and the alkyne is obtained by fractional distillation.

Method B: Aliquat (1.0 g, 2.5 mmol) and anhydrous pinacol (1.0 g, 8.5 mmol) are added to powdered KOH (50.5 g, 0.9 mol) suspended in petroleum ether (b.p. >170°C, 20 ml). The mixture is stirred at 130°C and the dihaloalkane (0.05 mol) is added. The alkyne distils from the reaction mixture.

Method C: The liquid dibromoalkane (0.5 mol) is added to powdered KOH (28 g, 0.5 mol), TOA-Br (0.55 g, 1 mmol) and $\text{Me}_2\text{C}(\text{OH})(\text{CH}_2)_2\text{CMe}_2\text{OH}$ (0.29 g, 2 mmol). The reaction is exothermic and, when complete, the alkyne (65–80%) is distilled from the mixture.

Method D: The liquid *vic*-dibromoalkane (10 mmol) is shaken with Aliquat (0.2 g, 0.5 mmol) and *t*-BuOK (2.8 g, 25 mmol) for 10 min at room temperature and then left for *ca.* 2 h. Et_2O (50 ml) is added and the mixture is filtered through Florisil. Evaporation of the filtrate yields the alkyne.

The catalysed β -elimination of hydrogen bromide from 2-bromoethyl and 1,2-dibromoethyl sulphides, using **9.1.1** or **9.1.2**, provides a convenient route to vinyl and alkynyl sulphides, respectively [17, 18], which, as their sulfoxides or sulphones, have considerable utility as dienophiles. Aryl vinyl ethers (>90%) have been obtained by analogous procedures from 2-chloroethyl ethers [19].

1,1-Dichloroalk-1-enes, which can be obtained by the Wittig reaction, are converted in good yield into the 1-chloroalk-1-yne under liquid:liquid [20] or solid:liquid two-phase conditions [21]. Elimination of HBr from 1,1-dibromoprop-1-enes using Triton-B in the presence of dialkylamines yields 3-aminoprop-1-yne, via the intermediate 1-bromoallene [22]. Tetra-ethylammonium fluoride has been used as the base for the elimination of halogen acids from 2-halogeno-2-(4-nitrophenyl)prop-1-enes and β -halo-4-nitrostyrenes [23]. *Anti*-elimination is preferred and, in the case of the propenes, allene intermediates are formed from the *E*-isomers.

9.1.3 1-Chloroalk-1-yne from 1,1-dichloroalk-1-enes

Method A (liquid:liquid conditions): In an apparatus flushed with argon and fitted with cold traps maintained at -35°C , $\text{CH}_2=\text{CCl}_2$ (4.8 g, 50 mmol) is added dropwise over 30 min via a syringe to aqueous NaOH (50%, 20 ml) and TBA- HSO_4 (0.4 g, 1.2 mmol) at 35°C under a flow of argon (20 ml/min). Further aliquots of the ethene (2.4 g) are added after 30, 60 and 90 min. The mixture is stirred for a further 90 min and $\text{CH}\equiv\text{CCl}$ (46%) is collected in a trap containing *n*- C_6H_{14} .

Method B (solid:liquid conditions): The 1,1-dichloroalkene (1 mmol), powdered KOH (1 mmol) and Aliquat (0.2 ml/g of dichloroalkene) are stirred and heated at 90°C for *ca.* 2 h. The alkyne [e.g. $\text{Me}(\text{CH}_2)_x\text{C}\equiv\text{CCl}$ $x = 3, 50\%$; 5, 80%; 6, 80%; 7, 90%; 10, 90%] is distilled directly from the reaction mixture.

E-2-bromomethyleneglutaric esters (>70%) have been obtained from the corresponding 2-bromo-2-bromomethylglutarates using a 25% excess tetra-*n*-butylammonium fluoride in HMPA [24]. A similar procedure converts dimethyl 2-bromo-2-bromomethylsuccinate into dimethyl *Z*-2-bromomethylenefumarate [25], whereas methyl 2,2-bis(bromomethyl)ethanoate yields the 2-bromomethylpropenoate when reacted with aqueous sodium hydroxide in the presence of benzyltriethylammonium chloride [26]. No hydrolysis of the ester is evident at 0°C, but becomes apparent at 25°C.

9.1.4 Dialkyl *E*-2-bromomethyleneglutarates

TBA-F.3H₂O (23.6 g, 75 mmol) in HMPA (40 ml) is cooled to 0°C and the appropriate 2-bromo-2-bromomethylglutarate (60 mmol) is added over 30 min. The reaction mixture is stirred at 0°C for a further 1 h and then allowed to come to room temperature. H₂SO₄ (2 M, 120 ml) is then added and the mixture is extracted with *n*-C₆H₁₄ (5 × 80 ml). The extracts are washed well with H₂O to pH 7, dried (MgSO₄), and fractionally distilled to yield the bromomethylene derivative.

9.1.5 Methyl 2-bromomethylpropenoate

Aqueous NaOH (1M, 50 ml) is added to (BrCH₂)₂CHCO₂Me (9.9 g, 38 mmol) and TEBA-Cl (50 mg, 0.2 mmol) in CCl₄ (50 ml) at 0°C and the mixture is stirred for 1 h. The organic phase is separated and the aqueous phase is extracted with CCl₄ (2 × 25 ml). The combined organic solutions are dried (MgSO₄) and evaporated to yield CH₂=C(CH₂Br)CO₂Me.

Cyclic ketene acetals, which have utility as co-polymers with functional groups capable of cross-linking, etc., have been prepared by the elimination of HX from 2-halomethyl-1,3-dioxolanes. Milder conditions are used under phase-transfer conditions, compared with traditional procedures, which require a strong base and high temperatures. Solid:liquid elimination reactions frequently use potassium *t*-butoxide [27], but acceptable yields have been achieved with potassium hydroxide and without loss of any chiral centres. The added dimension of sonication reduces reaction times and improves the yields [28, 29]. Microwave irradiation has also been used in the synthesis of methyleneacetals and dithioacetals [30] and yields are superior to those obtained with sonofication.

Diol monoacetates are obtained from the diols via the intermediate formation of the bromomethyl acetals and their conversion into cyclic methylene acetals, which undergo acid-catalysed ring-opening to yield the acetate ester [31]. The ring-opening is regio-specific to form the ester at the least hindered hydroxyl group.

9.1.6 Solid:liquid formation of methylene ketals

Method A (without sonication): Powdered *t*-BuOK (2.25 g, 20 mmol) is added portion-wise with stirring to the halomethyl ketal (10 mmol) and Aliquat (80 mg, 0.2 mmol) in THF (10 ml) at 0°C. The mixture is allowed to stand at 0°C for *ca.* 2 h and is then

brought to room temperature and Et₂O (50 ml) is added. The mixture is filtered through alumina and then evaporated to yield the methylene ketal (e.g. 2-methylene-4,5-diphenyl-1,3-dioxolane, 89%; 2-methylene-1,3-dioxep-5-ene, 68%; 2-methylene-4-vinyl-1,3-dioxolane, 43%).

Method B (with sonication): The bromomethylacetal (0.1 mol) and powdered KOH (11.2 g, 0.2 mol) with TBA-Br (0.64 g, 2 mmol) are subjected to sonication (50 KHz, 200 W) for 1 h at 75°C. Fractional distillation yields the methylene ketal [e.g. 2-methylene-1,3-dioxolane, 68%; 2-methylene-4-phenyl-1,3-dioxolane, 81% (68%); 2-methylene-4,5-diphenyl-1,3-dioxolane, 87%; 2-methylene-7,9-dioxabicyclo[4.3.0]nonane, 61% (36%); 2-methylene-1,3-dioxepane, 79% (63%); 2-methylene-1,3-dioxep-5-ene, 70% (41%); 4-methylene-2-phenyl-1,3-dioxolane, 93%].

Method C (under microwave irradiation): The halomethylacetal (or dithioacetal) (2 mmol), TBA-Br (32 mg, 0.1 mmol) and *t*-BuOK (0.55 g, 5 mmol) are irradiated at 75 W for 25 min at 60–80°C in a microwave reactor to yield on work-up the methylene acetal [e.g. 2-methylene-4-phenyl-1,3-dioxolane, 87%; 2-methylene-1,3-dioxep-5-ene, 82%; 1,1-di-(butylthio)ethene, 79%; 1-methoxy-1-phenylthioethene, 90%].

9.1.7 One-pot conversion of bromomethyl cyclic acetals into diol monoacetates

The 2-bromoacetal (0.1 mol), prepared by the Dowex X8 (H⁺)-catalysed reaction of the diol with 1-bromo-2,2-dimethoxyethane, is added to *t*-BuOK (16.8 g) and Aliquat (0.81 g, 2 mmol) in THF (150 ml) and the mixture is stirred at 80–90°C until the reaction is complete (2–4 h). *n*-C₅H₁₂ (4 × 200 ml) is added portionwise, with stirring after each addition, and the reaction mixture is then filtered through alumina. The filtrate is concentrated, H₂O (5.5 ml) and AcOH (*ca.* 0.2 ml) are added to the residue, and the solution stirred at room temperature for 3 min. The aqueous mixture is extracted with Et₂O (3 × 20 ml) and the extracts are dried (Na₂SO₄) and evaporated to yield the diol half ester [e.g. AcO(CH₂)₂OH, 70%; AcO(CH₂)₄OH, 85%; MeCH(OH)(CH₂)₂OAc, 80%; MeCH(OAc)CH₂CMe₂OH, 85%].

The reductive dehalogenation of *vic*-dibromides to give the alkenes, using sodium sulphide [32] or sodium trithiocarbonate [33] is aided by the addition of quaternary ammonium salts. *Anti*-elimination normally occurs in good yield, but is susceptible to steric factors [34]. Other functional groups are not reduced by the sulphide.

9.1.8 Reductive dehalogenation of *vic*-dibromides (Table 9.2)

Method A: Na₂S.9H₂O (2.65 g, 11 mmol) in H₂O (10 ml) is added the dibromoalkane (5 mmol) and Aliquat or TEBA-Cl (0.5 mmol) in PhH (10 ml)*. The initially exothermic reaction is stirred for *ca.* 1 h at room temperature and the organic phase is then separated, washed with H₂O (2 × 20 ml), dried (MgSO₄), and evaporated to yield the alkene. Gaseous alkenes are collected using a gas burette (* the solvent can be omitted with liquid dihaloalkanes).

Method B: Aqueous Na₂CS₃ (30%, 3 ml, 6 mmol) and Aliquat (32 mg, 0.08 mmol) are added to the dibromoalkane (2 mmol) in PhH (5 ml) and the mixture is stirred at room temperature and the reaction is monitored by the decolorization of the orange solution.

TABLE 9.2

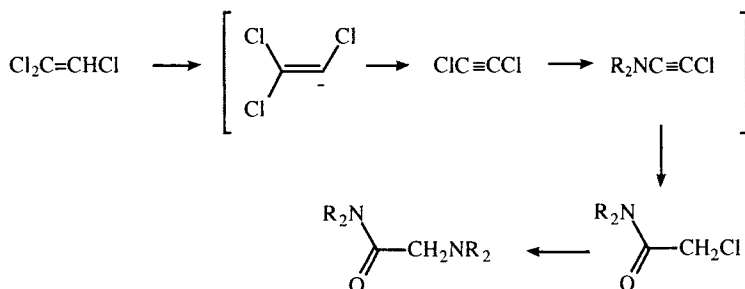
Selected examples of the reductive dehalogenation of *vic*-dibromides

Dibromo compound	Reaction conditions	Product	% yield
<i>ms</i> -PhCHBrCHBrPh	9.1.8.A/1 h	<i>trans</i> -PhCH=CHPh	93
	9.1.8.B/10 min	<i>trans</i> -PhCH=CHPh	100
<i>dl</i> -PhCHBrCHBrPh	9.1.8.A/1 h	<i>trans</i> -PhCH=CHPh	15
		<i>cis</i> -PhCH=CHPh	81
	9.1.8.B/5 h	<i>trans</i> -PhCH=CHPh	19
		<i>cis</i> -PhCH=CHPh	76
PhCHBrCH ₂ Br	9.1.8.B/1 h	PhCH=CH ₂	78
PhC(Me)BrCH ₂ Br	9.1.8.A/30 min	Ph(Me)C=CH ₂	73 ^a
1,2-Br ₂ -cyclo-C ₆ H ₁₀	9.1.8.A/2 h	cyclo-C ₆ H ₁₀	90 ^b
1,2-Br ₂ -cyclo-C ₈ H ₁₄	9.1.8.A/2 h	cyclo-C ₈ H ₁₄	60 ^b
<i>n</i> -C ₉ H ₁₉ CHBrCH ₂ Br	9.1.8.A/1 h	<i>n</i> -C ₉ H ₁₇ CH=CH ₂	12 ^c
<i>n</i> -C ₁₀ H ₂₁ CHBrCH ₂ Br	9.1.8.A/2 h	<i>n</i> -C ₁₀ H ₂₁ CH=CH ₂	72 ^b
MeCHBrCHBrMe	9.1.8.A/30 min	MeCH=CHMe	60 ^b
PhCHBrCHBrCOMe	9.1.8.A/1 h	PhCH=CHCOMe	84
PhCHBrCHBrCO ₂ Et	9.1.8.B/1 h	PhCH=CHCO ₂ Et	94

^a In *n*-C₅H₁₂. ^b No solvent. ^c Plus nucleophilic substitution products.

The organic phase is separated, washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the alkene.

In an interesting catalysed conversion of trichloroethene by secondary amines into aminoacetamides, the initial steps are thought to involve the β-elimination of HCl to produce dichloroethyne (Scheme 9.1), which reacts with the secondary amine under the 'wet' conditions to produce the amide [35]; the reaction does not work with *N*-alkylanilines. Such a mechanism is realistic, as it is well known [36] that trichloroethene is converted into the inflammable and explosive dichloroethyne by bases, and quaternary ammonium salts catalyse the formation of the alkyne when trichloroethene is reacted with oxiranes [37]. Chloroethynes have also been obtained by the catalysed reaction of terminal ethynes with carbon tetrachloride under basic conditions [38].

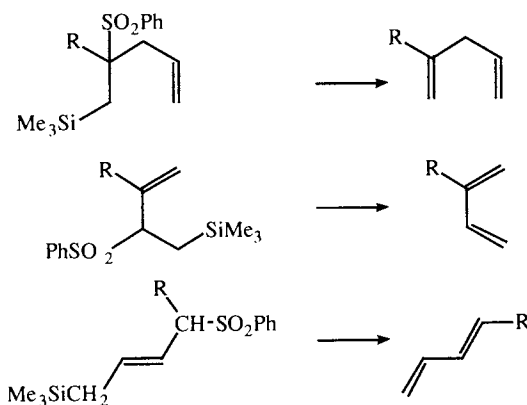


Scheme 9.1

9.1.9 Conversion of trichloroethene into aminoacetamides

NaOH (50 g, 1.25 mol) in H₂O (50 ml) and the secondary amine (0.5 mol) with TEBA-Cl (1.1 g, 5 mmol) are stirred and heated to 70°C. Cl₂C=CHCl (22.5 ml, 0.25 mol) is added dropwise at 70–100°C (external cooling may be necessary). The mixture is refluxed for 1 h and the H₂O is then removed under reduced pressure. The residue is extracted with CH₂Cl₂ (500 ml) and the extract is dried (Na₂SO₄) and evaporated to yield the amide R₂NCH₂CONR₂ (e.g. R₂N = Me₂N, 51%; *n*-Bu₂N, 81%; Et₂N, 79%; morpholinyl, 71%; piperidinyl, 83%).

Quaternary ammonium fluorides have widespread use, often in stoichiometric ratios, as a base or for cleavage of silyl protecting groups. Tetra-*n*-butylammonium fluoride promotes the concomitant elimination of benzenesulphonyl and trimethylsilyl groups to produce alkenes [39] and dienes [39, 40] (Scheme 9.2) and a similar elimination of benzenesulphonyl and tributyltin groups [41, 42], which is preferred for sterically hindered systems, has also been reported. The driving force in the fluoride ion promoted elimination of phosphonyl and fluoride substituents from RCF=CHPO(OEt)₂, catalysed by tetra-*n*-butylammonium fluoride, to yield alkynes is probably the favourable energetics of the formation of the P-F bond [43].



Scheme 9.2

Concomitant C-Si cleavage by tetra-*n*-butylammonium fluoride and extrusion of a phenylthiolate anion from α -trialkylsilyl disulphides provides a route to reactive thioaldehydes [44].

9.1.10 Thioaldehydes

TBA-F in THF (0.01 M, 200 ml) is added slowly with stirring over 30–60 min to the α -silyl disulphide RCH(SiR₃)SSAr (5 mmol). The mixture is stirred until all of the disulphide is consumed and the reactive thioaldehyde is reacted *in situ* without isolation.

Dehydration of *N,N'*-disubstituted ureas with 4-tosyl chloride under solid:liquid two-phase conditions to produce carbodiimides is aided by the addition of benzyltriammonium chloride [45, 46].

9.1.11 Carbodiimides from ureas

The *N,N'*-disubstituted urea (10 mmol) and TosCl (1.9 g, 10 mmol) in PhMe (70 ml) are stirred under reflux with K_2CO_3 (3.53 g) and TEBA-Cl (0.23 g, 1 mmol). When the reaction is complete, as indicated by TLC analysis, the mixture is filtered and the filtrate is washed with H_2O (2×10 ml), dried ($MgSO_4$), and evaporated to yield the carbodiimide (Table 9.3).

TABLE 9.3

Selected examples of the solid:liquid dehydration of *N,N'*-disubstituted ureas with 4-toluenesulphonyl chloride

RNHCONHR'		Reaction conditions	% yield
R = cyclo- C_6H_{11}	R' = cyclo- C_6H_{11}	9.1.11/11 h ^a	35
<i>t</i> -Bu	<i>t</i> -Bu	9.1.11/13 h ^a	30
<i>n</i> -Bu	$PhCH_2$	9.1.11/4 h ^b	96
cyclo- C_6H_{11}	$(CH_2)_3NMe_2$	9.1.11/1 h ^c	85
cyclo- C_6H_{11}	$(CH_2)_3(NC_5H_{10})$	9.1.11/1.2 h ^d	86
Ph	$(CH_2)_3NMe_2$	9.1.11/4 h ^b	68

^a In $CHCl_3$, ^b In PhH, ^c In $CHCl_3$:PhH (1 : 2), ^d In PhMe.

Thioamides are converted into *S*-benzyl salts under basic catalysed conditions. The unstable salts spontaneously eliminate benzythiol to yield nitriles (>80%) [47]; the benzythiol is benzylated during the reaction and is isolated as dibenzyl sulphide.

9.1.12 Conversion of thioamides into nitriles

The thioamide (10 mmol), $PhCH_2Cl$ (2.53 g, 20 mmol), TBA-Br (16 mg, 0.05 mmol) are stirred in PhH (70 ml) and aqueous NaOH (30%, 50 ml) at 30°C for *ca.* 2 h until the reaction is complete, as shown by GLC analysis. The aqueous phase is separated and extracted with PhH (2×25 ml). The combined organic solutions are dried (Na_2SO_4) and fractionally distilled to yield the nitrile [e.g. MeCN, 80%; EtCN, 94%; $PhCH_2CN$, 86%, PhCN, 91%].

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9.2 CLEAVAGE REACTIONS

Esters are hydrolysed under basic conditions in the presence of quaternary ammonium salts [e.g. 1–7]. Microwave activation of basic solid:liquid systems without an added solvent enhances the rate of saponification and the reaction is not affected by steric factors [3]. Microwave irradiation has also been used in the hydrolysis and decarboxylation of malonic esters [8] and β -keto esters [9] (>90%). Lactones

undergo acid-catalysed hydrolysis in the presence of benzyltriethylammonium chloride, for example, α -acetyl- γ -butyrolactone is converted into 5-bromopentan-2-one (85%) by 48% hydrobromic acid under liquid:liquid two-phase conditions [10].

9.2.1 Ester hydrolysis

Method A (liquid:liquid systems): The ester (25 mmol) in CH_2Cl_2 (10 ml) is stirred for *ca.* 12 h at 20°C with aqueous NaOH (50%, 2.5 ml) and TEBA-Cl (0.1 g, 0.4 mmol). The aqueous phase is separated, washed with CH_2Cl_2 (2 \times 10 ml) and acidified with dilute HCl. The carboxylic acid either precipitates or is extracted from the aqueous solution with Et_2O or CH_2Cl_2 .

Method B (solid:liquid systems): The ester (10 mmol) is shaken with powdered KOH (2.8 g, 50 mmol) and Aliquat (0.48 g, 1 mmol) for 5 min at room temperature and then left at 85°C until TLC analysis shows the hydrolysis to be complete. The mixture is acidified with aqueous HCl and the acid (>90%) is collected (if solid) or extracted with Et_2O or CH_2Cl_2 (if a liquid).

Method C (with microwave irradiation): An intimate mixture of the ester (25 mmol), Aliquat (1 g, 2.5 mmol) and powdered KOH (3.25 g) is subjected to microwave irradiation. On completion of reaction, the mixture is washed with CH_2Cl_2 and the residue is acidified with aqueous HCl. The carboxylic acid is isolated as described in 9.2.1.B [e.g. 87% from PhCO_2Me (30 sec); 83% from $\text{PhCO}_2\text{C}_8\text{H}_{17}$ (1 min); 75% from 1,4,6- $\text{Me}_3\text{C}_6\text{H}_2\text{CO}_2\text{Me}$ (2 min)].

Method D (hydrolysis and decarboxylation of malonic esters and β -keto esters): LiBr (1.73 g), TBA-Br (0.32 g, 1 mmol), the malonic ester or β -keto ester (10 mmol) and H_2O (360 ml) are subjected to microwave irradiation for 15 min. The cooled mixture is extracted with EtOAc (50 ml) and the organic solution is filtered through Florisil and evaporated to yield the decarboxylated compound.

4,6-Dioxo-1,3-dioxanes ring-open under basic conditions. Cleavage of the 5,5-disubstituted derivatives in the presence of quininium or quinidinium alkoxides produces chiral malonic hemi-esters (ee 30–40%) in high yield [11]. The addition of cetyltrimethylammonium bromide promotes the base-catalysed cleavage of β -keto esters to form ketones under sonication [12].

9.2.2 Malonic hemi-esters

The ammonium catalyst (0.36 mmol) in dry THF (2 ml) is stirred with methanolic MeONa (20%, 0.11 ml) at room temperature. The mixture is stirred for 10 min and added to the Meldrum's acid derivative (0.3 mmol) in PhMe (13 ml) at -30°C. When the reaction is complete (*ca.* 5–10 min), as shown by GLC, it is quenched with aqueous citric acid (3%, 30 ml). The aqueous phase is separated, extracted with Et_2O (3 \times 20 ml), and the combined organic solutions are dried (MgSO_4) and evaporated at <50°C to yield the hemi-ester.

9.2.3 Cleavage of β -keto esters

The β -keto ester, $\text{MeCOCH(R)CO}_2\text{Et}$ (1 mmol) in PhMe (1 ml) is added to CTMA-Br (36 mg, 0.1 mmol) in aqueous KOH (10%, 5 ml) and the mixture is subjected to sonica-

tion at 80°C for 45 min. The mixture is acidified with H₂SO₄ (1M) and extracted with Et₂O (25 ml). The dried (MgSO₄) extract is evaporated to yield the ketone [e.g. R = *n*-Pr, 75%; PhCH₂, 90%; Ph(CH₂)₂, 90%].

t-Butyl α -trifluoroacetamidoacetates are hydrolysed to the corresponding amino esters under basic conditions in the presence of benzyltriethylammonium chloride [13]. The reaction is specific for the cleavage of the amido linkage without concomitant hydrolysis of *t*-butyl ester groups, although methyl and ethyl esters are hydrolysed under basic conditions [4, 5]. The procedure can be adapted to the synthesis of alkylamines, as an alternative to the Gabriel synthesis, and of dialkylamines; the intermediate trifluoroacetamides are hydrolysed with potassium hydroxide or reductively cleaved with sodium borohydride [14]. N-BOC-protected acylamides are selectively hydrolysed to the N-BOC amines under basic catalytic conditions [15]. A high-yielding one-pot *N*-alkylation and basic hydrolysis of 2-nitrotrifluoroacetanilides and subsequent reduction of the nitro group provides a convenient route to *N*-alkyl-*o*-phenylenediamines [16].

9.2.4 Selective *N*-deprotection of trifluoroacetamido esters

The CF₃CONHCH₂CO₂*t*-Bu (0.22 g, 1 mmol) and TEBA-Cl (23 mg, 0.1 mmol) in CH₂Cl₂ or Et₂O (5 ml) is stirred at 25°C with aqueous KOH (20%, 0.7 ml) and the hydrolysis is monitored by GLC analysis. The aqueous phase is separated, extracted with Et₂O (2 \times 5 ml) and the combined organic solutions are dried (MgSO₄) and evaporated. The residue is dissolved in Et₂O and HCl gas is bubbled through the solution for *ca.* 5 min at 0°C. The hydrochloride salt RCH(NH₃⁺Cl⁻)CO₂*t*-Bu precipitates [e.g. R = Me, 89% (18 h); *n*-Bu, 88% (4 days); C₁₀H₂₁, 95% (7 days); Ph, 88% (7 days); PhCH₂, 75% (24 h)].

9.2.5 Concomitant *N*-alkylation and hydrolysis of trifluoroacetanilides

Aqueous NaOH (50%, 10 ml) is added to the trifluoroacetanilide (10 mmol), TEBA-Cl (2.45 g, 10 mmol), and the haloalkane (12.5 mmol) in PhMe (20 ml) and the mixture is stirred at room temperature until TLC analysis indicates complete consumption of the anilide. Aqueous NH₄Cl (sat. soln., 20 ml) is added and the aqueous phase is separated and extracted with EtOAc (3 \times 20 ml). The combined organic solutions are dried (MgSO₄) and evaporated to yield the *N*-alkylaniline.

The cleavage of resin-bound peptides, produced in the Merrifield synthesis, is aided by the addition of quaternary ammonium salts to the basic medium [17, 18]. In many cases, cleavage is 100% effective and rarely less than 70%.

9.2.6 Cleavage of resin-bound peptides

Aqueous K₂CO₃ (sat. soln., 5 ml) and TBA-HSO₄ (0.68 g, 2 mmol) is added to a suspension of resin-bound peptide (1 g) in THF (50 ml). The mixture is stirred until cleavage is complete (up to 24 h) and H₂O (20 ml) is then added. The mixture is filtered and the residue is washed with H₂O (20 ml) and extracted with EtOAc (2 \times 30 ml). The organic

extracts are evaporated and the residue is taken up in minimum amount of H₂O. The pH of the aqueous solution is adjusted to 1.0 with KHSO₄ and the precipitated solid is collected, washed with H₂O (5 × 20 ml), and dried under vacuum to yield the peptide.

N-Sulphonyl azoles are deprotected by a stoichiometric amount of tetra-*n*-butylammonium fluoride in THF in good yields (>70%) [19].

9.2.7 Deprotection of *N*-methanesulphonyl- and *N*-arenesulphonylazoles (Table 9.4)

TBA-F (1.M in THF, 0.5 ml) is stirred under reflux with the *N*-sulphonylazole (0.5 mmol) in THF (20 ml). The mixture is cooled and the solvent evaporated under vacuum. H₂O (20 ml) is added to the residue and the mixture is extracted with Et₂O (2 × 20 ml). The extracts are dried (MgSO₄) and evaporated to yield the azole.

TABLE 9.4
Selected examples of the deprotection of *N*-sulphonyl azoles

Sulphonyl group	Azole	Reaction conditions	% yield
PhSO ₂	2-Formylpyrrole	9.2.7/6 h	90
PhSO ₂	2-Ethylpyrrole	9.2.7/24 h	64
TolSO ₂	4-Iodo-5-phenylpyrazole	9.2.7/30 min	100
PhSO ₂	2-Phenylindole	9.2.7/1.5 h	100
MeSO ₂	3-Formylindole	9.2.7/1 h	100
MeSO ₂	3-Acetylindole	9.2.7/2 h	91
MeSO ₂	2- <i>n</i> -Butylindole	9.2.7/5 h	89

Lewis acid-catalysed deprotection of enol ethers to yield carbonyl compounds is aided by the addition of tetra-*n*-butylammonium fluoride. Optimum yields were obtained with equimolar amounts of the enol ether in dichloromethane with the fluoride and boron trifluoride etherate [20, 21].

Oxiranes undergo nucleophilic ring-opening with a range of reagents under phase-transfer catalytic conditions. Simple reaction of the oxirane with tetra-*n*-butylammonium bromide in the presence of magnesium nitrate produces the bromoethanol (>90%) [22]; dihydrogen trifluoride salts produce fluorohydrins [23]. Generally, the catalysed reactions with nucleophiles are regiospecific with attack occurring at the less hindered carbon atom. Thus, aliphatic thiols, thiophenols and *S*-phenyl thioalkanoates yield β-hydroxyethyl thioethers and the corresponding β-acyloxy derivatives [24–26] (although ring-opening of oxetanes is not catalysed by quaternary ammonium salts, five-membered amide acetals react with the thioesters to yield ring-opened products [27]). Sodium azide reacts with ethoxycarbonyloxiranes (5.4.2.A) to produce ring-opened azido esters, which are catalytic-hydrogenated to give ethyl glycidates (~60%) [28]; β-Aminoethanols are obtained from the corresponding reaction of styrene oxide. Solid:liquid phase ring-opening of oxiranes

by haloalkanes under basic conditions produces alkyl ethers [29, 30] and reaction with trifluoroacetamide under solid:liquid conditions yields β -amido alcohols (55–75%) [31] with retention of chiral centres. Ring-opening is also achieved with the conjugate base of phenylacetonitrile in the presence of added lithium salts [32].

The analogous ring-opening of thiiranes with acyl chlorides produces *S*-(β -chloroethyl) thiocarboxylates [33].

9.2.8 Ring-opening of oxiranes (Table 9.5)

By PhSH: The oxirane (0.1 mol), PhSH (0.1 mol) and TBA-Br (1.61 g, 5 mmol) in diglyme (50 ml) are stirred at 90°C for *ca.* 5 h. Et₂O (100 ml) is added and the filtered organic solution is washed with H₂O (3 \times 50 ml), dried (MgSO₄), and evaporated to yield the β -hydroxyethyl thioether, PhSCH₂CH(OH)R (R = PhOCH₂, 78%; MeOCH₂, 67%).

By S-phenyl thioalkanoates. Method A: The oxirane (50 mmol) R¹COSPh (50 mmol), TBA-Br (1.61 g, 5 mmol) in DMF (50 ml) are stirred at 110°C until the reaction is complete. The ring-opened product is isolated as described for the corresponding reaction with PhSH to yield the β -acyloxyethyl thioether, PhSCH₂CH(OCOR¹)R² [R¹ = Me, R² = MeOCH₂, 60% (10 h); Me, PhOCH₂, 76% (10 h); Ph, MeOCH₂, 70% (50 h); Ph, PhOCH₂, 71% (25 h)].

Method B: using a polymer-supported trimethylammonium salt: The oxirane (10 mmol) and RCOSPh (10 mmol) in diglyme (5 ml) are added to the resin (\equiv 0.5 mmol $-NMe_3^+$ salt) and the mixture is stirred at 110°C for 24 h. The resin is removed and Et₂O (30 ml) is added to the filtrate. The ethereal solution is washed well with water, dried (MgSO₄), and evaporated to yield the β -acyloxyethyl thioether.

By haloalkanes: The oxirane (50 mmol) is stirred with the haloalkane (0.1 mol), NaOH (6 g) and TBA-HSO₄ (0.85 g, 2.5 mmol) in dioxan (20 ml) at 70–100°C for 0.75–3 h. The mixture is filtered and fractionally distilled to yield the ring-opened alkyl ether.

By CF₃CONH₂: The oxirane (1 mmol), K₂CO₃ (14 mg), TEBA-Cl (23 mg, 0.1 mmol), CF₃CONH₂ (0.22 g, 2 mmol) and dioxane (0.25 ml) are stirred at 90°C until the epoxide is no longer detectable by TLC analysis. The mixture is cooled to room temperature and CH₂Cl₂ (25 ml) is added. The mixture is filtered through Celite and the filtrate is evaporated to yield the β -amido alcohol, RCH(OH)CH₂NHCOCF₃ (e.g. R = Ph, 58%; CH₂OPh, 75%; CH₂OCH₂CH=CH₂, 55%; *n*-C₆H₁₃, 75%).

TABLE 9.5

Selected examples of ring-opening of oxiranes by chloroalkanes to yield allyl ethers

Chloroalkane (RCl)	Reaction conditions	% yield (ROCH ₂ CH=CHX)
<i>With epichlorhydrin</i>		<i>X = Cl</i>
PhCH ₂ Cl	70°C/0.75 h	50
ClCH ₂ C(Me)=CH ₂	90°C/0.75 h	27
Epichlorhydrin	70°C/3 h	38 ^a
<i>With (phenylthiomethyl)oxirane</i>		<i>X = SPh</i>
<i>n</i> -C ₈ H ₁₇ Cl	100°C/2 h	22
PhCH ₂ Cl	90°C/2 h	73
ClCH ₂ C(Me)=CH ₂	90°C/2 h	80

^a ClCH=CHCH₂OCH₂(C₂H₅O), no bis(oxirinylmethyl)ethers formed.

By PhCH_2CN : PhCH_2CN (1.17 g, 10 mmol) in PhH (2 ml) is added to TBA-F (0.31 g, 1 mmol), powdered KOH (0.53 g) and LiClO_4 (1.17 g) in PhH (4 ml). The mixture is stirred for 1 h at 60°C and the oxirane (10 mmol) is added dropwise over 30 min. The mixture is stirred for ca. 8 h, cooled to room temperature, and H_2O (10 ml) and PhH (10 ml) are added. The organic phase is separated and evaporated to yield the 1-cyano-3-hydroxy-1-phenylpropane.

By *tetra-*n*-butylammonium dihydrogen trifluoride*: The oxirane (1 mol), $\text{TBA-H}_2\text{F}_3$ (30.15 g, 0.1 mol) and KHF_2 (196 g) are stirred at 120°C until the oxirane is consumed. CH_2Cl_2 (50 ml) is added and the filtered solution is evaporated. The fluorohydrin is isolated by flash chromatography from silica [e.g. $\text{FCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$, 30 h, 47%; $\text{FCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OPh}$, 8 h, 90%; $\text{FCH}_2\text{CH}(\text{OH})\text{Ph}$, 8 h, 61% (+ 39% $\text{HOCH}_2\text{CHFPh}$); *erythro*- $\text{PhCH}(\text{OH})\text{CHFPh}$, 72 h, 71% from the *cis*-oxirane].

9.2.9 *S*-(β -Chloroethyl) thiobenzoates

The thiirane (5 mmol) and PhCOCl (0.7 g, 5 mmol) are shaken with TBA-Br (8 mg, 0.025 mmol) at 90°C and the thioester is isolated using a procedure analogous to that described in 9.2.8 (for PhSH).

Oxiranes undergo ring-opening with cerium(VI) ammonium nitrate and an excess of a quaternary ammonium halide to yield haloethanols [34]. The reaction occurs with high regio- and stereo-selectivity, for example, *R*(+)-styrene oxide produces *S*(+)-2-chloro-2-phenylethanol in 85% yield with 96% ee.

9.2.10 Cerium(VI) promoted ring-opening of oxiranes

CAN (1.64 g, 3 mmol) is added to the oxirane (10 mmol) and TBA-Br (9.67 g, 30 mmol) in MeCN (30 ml). The mixture is stirred at room temperature until GLC analysis indicates completion of the reaction. The solvent is evaporated and H_2O (30 ml) is added. The aqueous mixture is extracted with Et_2O (3×60 ml) and the extracts are evaporated to yield the 2-haloethanol [e.g. $\text{RCH}(\text{OH})\text{CH}_2\text{X}$: $\text{R} = \text{PhOCH}_2$, $\text{X} = \text{Cl}$, 93%; PhOCH_2 , Br, 95%; $\text{CH}_2=\text{CHCH}_2\text{OCH}_2$, Cl, 93% or $\text{RCH}(\text{X})\text{CH}_2\text{OH}$: $\text{R} = \text{Ph}$, $\text{X} = \text{Cl}$, 85%; Ph, Br, 92%; Me, Cl, 70%; Me, Br, 80%].

Aromatic and α -substituted aliphatic aldehydes react with oxiranes under neutral conditions to yield 1,3-dioxolanes [35] whereas α -unsubstituted aldehydes undergo a simple aldol condensation under such conditions. In a somewhat similar manner, perfluorocarboxylic esters react with oxiranes to produce cyclic orthoesters (~50%) [36]. The corresponding reaction with non-fluorinated esters fails.

9.2.11 1,3-Dioxolanes from oxiranes

The aldehyde (1 mol) and oxirane (1.1 mol) are heated in an autoclave with TEA-Br (2 g, 9.5 mmol) at 110°C for 3 h. The dioxolanes are isolated by fractional distillation (e.g. 85% from CH_2O ; 78% from Me_2CHCHO ; 75% from PhCHO).

9.2.12 Cyclic orthoesters from oxiranes (Table 9.6)

The oxirane (3 mmol), perfluorocarboxylic ester (3 mmol) and TBA-Br (48 mg, 0.15 mmol) are stirred at 90°C for 24–72 h. The mixture is extracted with CH₂Cl₂ (3 × 15 ml) and the combined extracts are washed well with H₂O, dried (MgSO₄), and fractionally distilled to yield the orthoester.

TABLE 9.6

Selected examples of the ring-opening of oxiranes with perfluorocarboxylic esters

Oxirane R(C ₂ H ₃ O)	Reaction conditions	% yield of orthoester
<i>With CF₃CO₂Et</i>		
R = CH ₂ OMe	9.2.12/72 h	67
CH ₂ =CHCH ₂ OCH ₂	9.2.12/72 h	71
PhOCH ₂	9.2.12/48 h	85
<i>With CF₃CF₂CO₂Et</i>		
R = PhOCH ₂	9.2.12/48 h ^a	50
<i>With CF₃(CF₂)₂CO₂Et</i>		
R = PhOCH ₂	9.2.12/48 h ^a	30

^a Using 0.25 mmol TBA-Br.

N-Arenesulphonylaziridines are cleaved by trimethyloxosulphonium salts under basic catalytic conditions with subsequent rearrangement to yield the correspondingly substituted azetidines (15–55%) [37].

The cleavage of benzyl ethers using hydrobromic acid is promoted by tetra-*n*-butylammonium bromide [38]. Selective cleavage of aryl silyl ethers can be effected in the presence of aliphatic silyl ethers using solid sodium hydroxide with tetra-*n*-butyl-ammonium hydrogen sulphate [39].

9.2.13 Debenzylation of benzyl phenyl ethers

The benzyl ether (0.69 mmol) in CH₂Cl₂ (5 ml) is added to TBA-Br (0.58 mg, 0.18 mmol) in aqueous HBr (46%, 1.3 ml) and mixture is refluxed for 24 h. The cooled mixture is diluted with CH₂Cl₂ (25 ml) and the organic phase is separated, washed well with H₂O, dried (Na₂SO₄), and concentrated. The phenol is isolated by chromatography of the concentrate (e.g. 2,6-Me₂C₆H₃OH, 66%; 3,5-Me₂-4-HOC₆H₂COMe, 53%; 3-MeO-5-Br-4-HOC₆H₂CHO, 63%; 3,5-Me₂-4-HOC₆H₃CO₂H, 87%).

9.2.14 Selective deprotection of aryl silyl ethers

The silyl ether (10 mmol), finely powdered NaOH (4 g, 0.1 mol) and TBA-HSO₄ (1.7 g, 5 mmol) in 1,4-dioxane (50 ml) are stirred under argon at room temperature for *ca.* 2.5–3 h, until TLC analysis indicates complete cleavage of the Si-O bond. The mixture is filtered through a bed of Celite and the filtrate is evaporated to yield the phenolic product (75–99%).

Efficient cleavage of *N,N*-dimethylhydrazones to yield the parent ketones (>90%) is effected under neutral conditions with tetra-*n*-butylammonium persulphate [40]. The procedure is particularly useful for compounds with acid-sensitive substituents, e.g. vinyl or ketal groups. Similarly, reaction times for the oxidative cleavage of semicarbazones with sodium nitrite or nitrate/trimethylsilyl chloride are reduced by the addition of benzyltriethylammonium chloride [41].

9.2.15 Oxidative cleavage of *N,N*-dimethylhydrazones

The hydrazone (0.5 mmol) in $\text{Cl}(\text{CH}_2)_2\text{Cl}$ (1 ml) is added to $(\text{TBA})_2\text{S}_2\text{O}_8$ (0.68 g, 1 mmol) in $\text{Cl}(\text{CH}_2)_2\text{Cl}$ (3 ml) and the solution is stirred under reflux. On completion of the reaction, the solution is poured into H_2O (20 ml) and the aqueous phase is separated and washed with CH_2Cl_2 (3×5 ml). The combined organic solutions are dried (MgSO_4) and evaporated to yield the ketone (e.g. cyclohexanone, 90%, 2-vinylcyclohexanone, 95%; cyclopentanone, 97%; PhCOMe , 90%; EtCOMe , 89%).

9.2.16 Oxidative cleavage of semicarbazones

Me_3SiCl (6.5 g, 60 mmol) in CCl_4 (10 ml) is added to the semicarbazone (30 mmol), NaNO_2 , or NaNO_3 (42 mmol), TEBA-Cl (0.34 g, 1.5 mmol) in CCl_4 (20 ml) and the mixture is stirred for 3 h at room temperature. The mixture is filtered through silica and evaporated to yield the carbonyl compound (e.g. EtCOMe , 78%; *t*- BuCOMe , 84%; cyclopentanone, 83%; cyclohexanone, 78%; PhCHO , 95%; PhCOMe , 80%; Ph_2CO , 88%).

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9.3 REARRANGEMENT REACTIONS

The Hofmann rearrangement of amides to yield isocyanates [1] or amines [2] can be induced under phase-transfer conditions using molecular bromine and a catalytic amount of a quaternary ammonium salt, or by stoichiometric amounts of benzyltriethylammonium tribromide. Isocyanates have been isolated without their hydrolysis to the amines, when bromine is used; prolonged reaction times favour the formation of ureas, the yields of which can be reduced at lower reaction temperatures (5°C) [1]. When the quaternary ammonium tribromide is used, yields of amines are generally good from both aromatic and aliphatic amides, although long chain aliphatic amides form acylureas [2].

Under more vigorous oxidative conditions, using a sodium hypochlorite/ammonium tribromide system, the initially formed amines, derived from substituted acetamides, are oxidized to nitriles (Scheme 9.3) [3].



Scheme 9.3

9.3.1 Hofmann degradation of amides (Table 9.7)

Method A: Br₂ (319.6 g, 2 mol) and aqueous NaOH (50%, 25 ml) are added to the amide (1.2 mol) and TBA-HSO₄ (1.7 g, 5 mmol) in CH₂Cl₂ (25 ml) at 25°C over 5–15 min. The organic phase is separated, dried (MgSO₄), and evaporated to yield the isocyanate.

TABLE 9.7
Selected examples of the Hoffman degradation of amides to isocyanates
(9.3.1.A) or amines (9.3.1.B)

RCONH ₂	Reaction conditions	% yield
R = Me	9.3.1.B/70°C/2 h	85
<i>n</i> -Pr	9.3.1.B/70°C/2 h	90
<i>n</i> -C ₅ H ₁₁	9.3.1.B/70°C/2 h	80
cyclo-C ₇ H ₁₃	9.3.1.A/rt/15 min	87
cyclo-C ₆ H ₁₁ (CH ₂) ₂	9.3.1.A/rt/15 min	86
1-Norbornyl	9.3.1.A/rt/15 min	76
PhCH ₂	9.3.1.B/70°C/3 h	75
1-NaphthylCH ₂	9.3.1.B/rt/5 h	51
Ph	9.3.1.B/rt/2 h	72
2-ClC ₆ H ₄	9.3.1.B/rt/2 h	86
4-ClC ₆ H ₄	9.3.1.B/rt/3 h	68
2-O ₂ NC ₆ H ₄	9.3.1.B/70°C/1 h	76
4-O ₂ NC ₆ H ₄	9.3.1.B/70°C/1 h	75
3-MeC ₆ H ₄	9.3.1.B/rt/2 h	93
3-Pyridyl	9.3.1.B/rt/70°C/5 h	44

Method B: The amide (5 mmol) and TEBA-Br₃ (1.95 g, 5 mmol) are added to aqueous NaOH (2.5M, 30 ml) and the mixture is stirred at room temperature until a brown colour persists. The mixture is steam distilled and the distillate is extracted with CH₂Cl₂ (4 × 40 ml). The combined extracts are dried (MgSO₄) and evaporated to yield the arylamine. Aliphatic amines are isolated by extraction of the reaction mixture with Et₂O and saturating the dried (MgSO₄) solution with HCl gas to produce the ammonium chlorides.

9.3.2 Oxidative Hofmann degradation of amides to nitriles

TBA-HSO₄ (0.12 g, 0.36 mmol) in PhH (5 ml) is added to NaBr (0.52 g) in aqueous NaOCl (6%, 6 ml) and the mixture is stirred at room temperature for 5 min. Na₃PO₄·12H₂O (1.25 g) in H₂O (5 ml) is added, followed by the acetamide (1.5 mmol). After an induction period of *ca.* 5 min, the temperature rises to *ca.* 40°C and stirring is continued until all of the amide has been consumed (*ca.* 45 min) and an interfacial layer has formed. The interfacial layer is separated, washed with brine (25 ml) and extracted with PhH (3 × 10 ml). The combined organic solutions are washed well with aqueous NaHSO₃ (10%) and NaHCO₃ (5%), dried (MgSO₄), and evaporated to give the nitrile (R = C₄H₉, 55%; C₈H₁₇, 60%; PhOCH₂CH₂, 60%; Ph 68%; 1-naphthyl, 55%; 2-naphthyl, 48%).

The Curtius rearrangement of acid chlorides to isocyanates (60–70%) is conveniently conducted under mild conditions using preformed tetra-*n*-butylammonium azide [4, 5].

9.3.3 Curtius rearrangement

NaN₃ (26 g) in H₂O (50 ml) is added to TBA-HSO₄ (67.9 g, 0.2 mol) in aqueous NaOH (10 M, 50 ml) and the solution is extracted with CH₂Cl₂ (2 × 100 ml). Evaporation at 40°C gives a quantitative yield of TBA-N₃, as a colourless oil.

The acid chloride (0.2 mol) in PhMe (150 ml) is added portionwise to TBA-N₃ (64.8 g, 0.2 mol) in PhMe (120 ml) at <25°C. The mixture is allowed to stand at room temperature for 4 h and is then heated. N₂ is evolved at 50–90°C and, when the evolution is complete, the unstable isocyanate is fractionally distilled. *In situ* reaction of the isocyanates with PhNH₂ gives the phenylureas (60–70%).

The Beckmann rearrangement of oximes to produce amides is promoted by perrhenate ions under phase-transfer catalytic conditions, in the presence of trifluoromethanesulphonic acid in nitromethane [6]. Under these conditions, the rearrangement reaction is frequently accompanied by the solvolysis of the oxime to the ketone. This can be obviated by the addition of hydroxylamine hydrochloride. No reaction occurs in the absence of the ammonium catalyst or with the *O*-acetyl oximes.

9.3.4 Perrhenate-catalysed Beckmann rearrangement of oximes (Table 9.8)

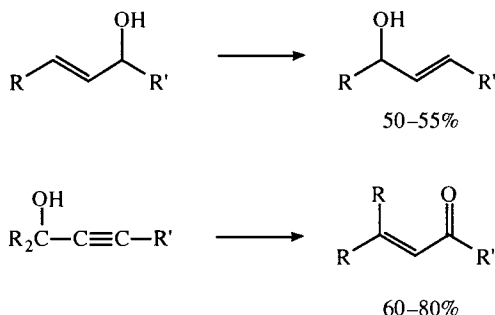
NH₂OH.HCl (15.2 mg, 0.21 mmol) is added to the oxime (1 mmol), TBA-ReO₄ (0.995 g, 0.2 mmol) and CF₃SO₃H (0.328 g, 0.21 mol) in MeNO₂ (6 ml) at room temperature. The mixture is refluxed under azeotropic conditions using 4 Å molecular sieves. Aqueous NaHCO₃ (sat. soln, 10 ml) is then added and the mixture is extracted with CH₂Cl₂ (3 × 15 ml). The extracts are washed with brine, dried (Na₂SO₄), and evaporated to yield the amide.

Table 9.8

Perrhenate-catalysed Beckmann rearrangement of oximes

R ¹ R ² C=NOH		Reaction time	Product	% yield
R ¹ = Ph	R ² = Ph	20 min	PhCONHPh	98
Ph	Me	1 h	MeCONHPh	94
PhCH ₂	Me	2 h	MeCONHCH ₂ Ph	88
PhCH ₂	PhCH ₂	40 min	PhCH ₂ CONHCH ₂ Ph	88
-(CH ₂) ₅ -		1.5 h	Caprolactam	84
-(CH ₂) ₂ CHPh(CH ₂) ₂ -		1 h	5-Phenylcaprolactam	91

The tautomerism of 1-nitroprop-1-enyl sugars into α,β-unsaturated oximes is catalysed by potassium fluoride in the presence of tetra-*n*-butylammonium hydrogensulphate, providing a route to 1,3-dicarbonyl sugar derivatives [7].



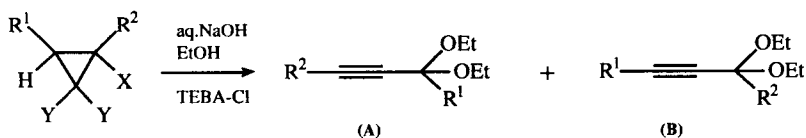
Scheme 9.4

Catalytic amounts of tetra-*n*-butylammonium perrhenate in the presence of 4-toluenesulphonic acid promote the rearrangement of allylic and propargylic alcohols (Scheme 9.4) via the intermediate formation of perrhenate esters [8, 9]. The corresponding rearrangement of propargyl chlorides with tetra-*n*-butylammonium copper(I) dichloride produces chloroallenes [10]. Allylbenzenes rearrange to produce styrenes, when heated with Adogen under basic conditions [11].

9.3.5 Rearrangement of allylic and propargylic alcohols

TBA-ReO₄ (16.6 mg, 0.033 mmol) and TosOH (3.3 mg) in CH₂Cl₂ (1.5 ml) are added to the unsaturated alcohol (0.33 mmol) in CH₂Cl₂ (2 ml) at room temperature. The mixture is stirred for 5 min* and Et₂O (10 ml) and aqueous NaHCO₃ (sat. soln, 10 ml) are added. The mixture is stirred for 5 min, and the organic phase is then separated, washed well with brine, dried (Na₂SO₄), and evaporated to yield the rearranged product (* longer reaction times in the production of dienes).

1,1,2-Trihalocyclopropanes, prepared from haloalkenes with dihalocarbenes under phase-transfer conditions, rapidly undergo a base-mediated ring-opening under liquid:liquid two-phase conditions in the presence of ethanol and benzyltriethylammonium chloride to yield isomeric 3,3-diethoxyprop-1-yne in moderate yields [12] (Scheme 9.5).



Scheme 9.5

9.3.6 Acetylenic acetals (Table 9.9)

Aqueous NaOH (50%, 6.5 ml) is added to the trihalocyclopropane (10 mmol), TEBA-Cl (0.2 g, 0.9 mmol), and EtOH (1.83 g, 40 mmol) in CH₂Cl₂ (15 ml) at room temperature and the mixture is stirred at room temperature until GLC analysis shows complete consumption of the cyclopropane. H₂O (10 ml) is added and the mixture is extracted with Et₂O (3 × 15 ml). The ethereal solutions are dried (MgSO₄) and evaporated to yield the alkyne.

1-Methylindene undergoes rapid rearrangement to 3-methylindene [13] via the conjugate base, when treated with aqueous sodium hydroxide and benzyltriethylammonium chloride under reaction conditions similar to those described in 9.4.1.

The [2,3] sigmatropic Wittig reaction, as exemplified by the rearrangement of fluorenyl allyl ethers under solid:liquid basic conditions is catalysed by tetra-*n*-butylammonium bromide [14].

Table 9.9
Selected examples of acetylenic acetals from 1,1,2-trihalocyclopropanes

Cyclopropane				% yield of acetylenic acetal	A:B ratio (Scheme 9.5)
R ¹	R ²	Y	X		
H	H	Br	Br	70	—
H	H	Cl	Br	57	—
H	Me	Br	Br	80	1 : 1
H	Me	Br	Cl	50	>9 : 1
H	Me	Cl	Br	64	1 : 1
H	Me	Cl	Cl	40	>20 : 1
Me	H	Br	Br	80	1 : 1
Me	H	Cl	Cl	39	>40 : 1
Me	Me	Br	Br	80	—
Me	Me	Cl	Cl	44	—

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9.4 HYDROGEN ISOTOPE EXCHANGE REACTIONS

The base-catalysed exchange of the α -protons of methylene ketones benefits from the addition of the quaternary ammonium salts [1, 2] and $^1\text{H}/^2\text{H}$ exchange of carbon acids with pK_a values >25 , which would normally require strong bases under anhydrous conditions, is facilitated by the addition of the ammonium salt to a solid:liquid two phase system [3–6], as is the $^1\text{H}/^2\text{H}$ exchange of electron-deficient aromatic and heteroaromatic ring hydrogen atoms [e.g. 4, 7] (Table 9.10). 1,2- and 1,3-Halobenzenes undergo *ca.* 30–40% exchange after 20 hours at room temperature, whereas $>75\%$ exchange is obtained for 1,4- and 1,3,5-substituted systems [4]. Although thiazoles undergo exchange of the hydrogen atom at C-2 and C-5 [8],

imidazole is unreactive [7, 9]. Pyridines are also less reactive [9]; 2-acetyl- and 2-dimethylaminopyridine exchange the hydrogen atom at C-6 at 50 °C (respectively, 13% after 3 hours and 19% after 1 h), whereas it is the methyl groups of 3-nitro-2, 6-dimethylpyridine which are exchanged (>70%) under similar reaction conditions [7]. Terminal deuterium and tritium exchange of 1-alkynes has been effected under mildly basic aqueous conditions at 20 °C under the influence of tetra-*n*-butylammonium bromide [10].

Table 9.10

Selected examples of phase-transfer catalysed $^1\text{H}/^2\text{H}$ exchange reactions

Substrate exchange	Reaction conditions	%
$\text{XC}_6\text{H}_4\text{Me}$		
X = 2-Cl	9.4.1/rt/20 h	44 ^a
2-Br	9.4.1/rt/20 h	62 ^a
2-NO ₂	9.4.1/rt/20 h	80 ^a
4-Cl	9.4.1/rt/20 h	5 ^a
4-Br	9.4.1/rt/20 h	11 ^a
4-NO ₂	9.4.1/rt/20 h	16 ^a
PhCH_2Ph	9.4.1/rt/20 h	73 ^b
Indene	9.4.1/rt/20 h	95 ^c
Fluorene	9.4.1/rt/20 h	98 ^b
Xanthene	9.4.1/rt/20 h	80 ^b
Thioxanthene	9.4.1/rt/20 h	79 ^b
Benzo[b]furan	9.4.3A/rt/20 h	(C-1) 88 (C-2) 52
Benzo[b]thiophene	9.4.3A/rt/20 h	(C-1) 76 (C-2) 26
Thiophene	9.4.3A/rt/20 h	(C-1) 91 (C-2) 12
2-Nitrothiophene	9.4.3B/50 °C/1 h	(C-5) 84
5-Ethylthiazole	9.4.3B/50 °C/1 h	(C-2) 90 ^d

^a Exchange of methyl hydrogen atoms. ^b Exchange of benzylic hydrogen atoms.^c 1,1,3-Trideuteroindene. ^d With TBA-Br. 90% at C-2 + 8% at C-4 with Aliquat.

9.4.1 Benzylic hydrogen exchange

The benzylic compound (1.5 mmol) and TBA- HSO_4 or TEBA-Cl (0.3 mmol) in PhH or CH_2Cl_2 (1.5 ml) are stirred at room temperature under Ar with a paste of NaOD in D_2O (60–63% w/w, 2:1 molar ratio for each hydrogen to be exchanged). On completion of the reaction, the mixture is extracted with CH_2Cl_2 (3 × 20 ml) and the extracts are washed with H_2O (10 ml), dried (MgSO_4), and evaporated to yield the deuterated product.

9.4.2 CH exchange on thioacetals

K_2CO_3 (0.5 g) is added to the thioacetal (1 mmol) and Aliquat (0.4 g, 1 mmol) in the PhMe (3 ml) and the mixture is stirred for 4 h at 50 °C. The filtered solution is shaken

with D₂O (0.1 ml) for 10 min. The organic phase is separated, and fractionally distilled to yield the deuterated product (70–90%).

9.4.3 Exchange of aromatic and heteroaromatic hydrogen atoms

Method A: The aromatic compound (2 mmol) and TBA-HSO₄ (0.14 g, 0.4 mmol) in *n*-C₆H₁₄ (1 ml) are stirred with a paste of NaOD in D₂O (60–63%, 1.1 g) for *ca.* 20 h at room temperature. The deuterated product is isolated, as described in **9.4.1**.

Method B: The aromatic compound (4 mmol) and TBA-Br or Aliquat (0.12 mmol) in C₆D₆ (2.5 ml) is stirred with NaOD in D₂O (10 M, 2 ml) at 50°C for 1 h. The deuterated product is isolated, as described in **9.4.1**.

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Oxidation of Organic Compounds

10.1 INTRODUCTION

The oxidation of organic compounds by water-soluble inorganic oxidants is often made difficult not only by the insolubility of the organic substrate in water, but also by the susceptibility of many of the miscible non-aqueous solvents to oxidation. Solubilization of the ionic oxidant into solvents such as benzene, chloroform, dichloromethane or 1,2-dichlorobenzene, by phase-transfer catalysts obviates these problems, although it has been suggested that dichloromethane should not be used, as it is also susceptible to oxidation [1].

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10.2 PERMANGANATE OXIDATIONS

The use of potassium permanganate as an oxidizing agent in organic synthesis has been reviewed up to 1986 with a summary of its application under phase transfer conditions [1]. The permanganate anion forms strong ion-pairs with many quaternary ammonium cations and, for example, relatively low concentrations of tetra-*n*-butylammonium salts are required for the efficient transfer of the permanganate anion into an organic solvent [2–4].

Solid tetra-*n*-butylammonium permanganate and benzyltriethylammonium permanganate have been prepared by simple extraction into an organic solvent using the appropriate quaternary ammonium salt and an inorganic permanganate salt in a stoichiometric ratio of slightly greater than 2 : 1, followed by evaporation of the organic solvent [see, e.g. 5]. Caution should be exercised, however, as all solid quaternary ammonium permanganates have decomposition temperatures of between 90 and 120°C and, although there are conflicting reports on their thermal stability, all quaternary ammonium permanganate salts should be treated as potentially

EXPLOSIVELY UNSTABLE compounds [4, 6–9]. It has been reported that solid benzyltriethylammonium permanganate is considerably less stable than the tetrabutylammonium salt; both compounds are sensitive to impact, but the benzylammonium salt may explode violently at room temperature [4] and it is more readily handled by absorption on alumina [4].

Under acidic conditions, tertiary amines also act as catalysts [10], the permanganate anion being probably transferred as $[R_3NH^+MnO_4^-]$. Although substituted toluenes are converted into the corresponding benzaldehydes in good yields (60–80%), little synthetic use appears to have been made of the system. Organic solutions of arsonium and phosphonium permanganates have also been prepared [1, 9, 11].

Organic solutions of tetra-alkylammonium permanganates, produced under liquid:liquid conditions, have the same characteristics as neutral or basic aqueous solutions of potassium permanganate, and manganese dioxide will be precipitated during the course of the oxidation reaction. The formation of the manganese dioxide can be controlled by adjusting the pH of the aqueous phase, either using quaternary ammonium hydrogen sulphates, or with dilute sulphuric, phosphoric or acetic acid. Under the acidic conditions, two-phase oxidation reactions, which are extremely slow in the absence of the catalyst, proceed rapidly and, in many cases, exothermically.

Alk-1-enes and aryl alkenes are oxidized to produce the carboxylic acid appropriate to the cleavage of the double bond, together with trace quantities of the lower homologues [e.g. 2, 5, 12–15]; the formation of the lower homologues is reduced by increasing the pH of the aqueous phase [13]. Under basic or neutral conditions, non-terminal alkenes are oxidized to yield the vicinal diols [3, 16–19] (Table 10.1) the kinetics of which have been studied [19], or aldehydes [20]. Fluoroalkenes are oxidized to the diols (75–85%) [21]. In the case of the oxidation of *endo*-dicyclopentadiene under solid:liquid conditions, the diol is obtained at high pH, whereas at lower pH (~3) cleavage of the C–C bond produces the dialdehyde [22, 23] and not the acid which is more normal [3, 16]. Also of interest is the catalysed oxidation of the Diels–Alder adduct derived from benzyne and 2,5-dimethylfuran, which gives 1,2-diacetylbenzene in 69% yield [24].

TABLE 10.1

Selected examples of the oxidation of alkenes to *cis*-1,2-diols

Alkene	Reaction conditions	% yield of diol
cyclo-C ₆ H ₁₀	10.2.2.C/1 h	86
cyclo-C ₈ H ₁₄	10.2.2.C/1 h	73
cyclo-C ₁₂ H ₂₂	10.2.2.B/5 h	65
cycloocta-1,5-diene	10.2.2.B/1 h	35 ^a
<i>n</i> -C ₈ H ₁₇ CH=CH ₂	10.2.2.B/2 h	85
PhCH=CHPh	10.2.2.B/30 min	70 ^{b,c}

^a *cis*-1,2-dihydroxycyclooct-5-ene. ^b benzaldehyde. ^c PhCH(OH)CH(OH)Ph is oxidized to PhCHO (97%) under similar conditions.

Generally, the yields of the diols are comparable with those obtained by the classical osmium tetroxide procedure, but are lower when the diol has a high degree of solubility in water. Under such circumstances, further oxidative cleavage occurs in the aqueous phase to produce the carboxylic acids [18]. The kinetics and mechanism of the oxidation of α,β -unsaturated carboxylic acids with permanganate in the presence of phase-transfer catalysts has been studied [25].

10.2.1 Typical preparation of quaternary ammonium permanganate salts

An excess of a quaternary ammonium salt (22 mmol) in H_2O (100 ml) is added to KMnO_4 (3.17 g, 20 mmol) in H_2O (200 ml). The mixture is stirred for *ca.* 30 min and the crystalline quaternary ammonium permanganate, which separates, is collected, and dried at room temperature under vacuum [TEBA- MnO_4 (95%), m.p. 127–129°C (decomp.); TBA- MnO_4 (>90%), m.p. 120–121°C; CTMA- MnO_4 (>85%); TBMA- MnO_4 (90%)].

10.2.2 *cis*-Hydroxylation of alkenes

Method A: Solid KMnO_4 (15.8 g, 0.1 mol) is added over a period of *ca.* 2 h with stirring to the alkene (0.1 mol) and Adogen (3 g, 6.7 mmol) in CH_2Cl_2 (100 ml) and aqueous NaOH (40%, 100 ml). The mixture is stirred for *ca.* 1 h and the precipitated MnO_2 is dissolved by the addition of aqueous NaHSO_3 (sat. soln.), or by a stream of SO_2 . Et_2O (500 ml) is added. The aqueous phase is separated and extracted with Et_2O (3×150 ml). The dried (MgSO_4) ethereal solutions are evaporated to yield the *cis*-diol.

Method B: CTMA- MnO_4 (2.02 g, 5 mmol) in CH_2Cl_2 (30 ml) is added dropwise to the alkene (5 mmol) in CH_2Cl_2 (15 ml) at 20°C. The mixture is stirred for 1–5 h and then concentrated to half volume. Et_2O (50 ml) is added and the solution is filtered through Celite and MgSO_4 . Evaporation of the filtrate yields the diol.

Method C: CTMA- MnO_4 (2.02 g, 5 mmol) in *t*-butanol (20 ml) and H_2O (5 ml) is added dropwise to the alkene (5 mmol) in *t*-butanol (5 ml) at 20°C. The mixture is stirred for 1–5 h and CHCl_3 (50 ml) and aqueous NaOH (5%, 15 ml) is then added. The two-phase system is stirred for 30 min, and the aqueous phase is then separated and extracted with CHCl_3 (3×50 ml). The combined CHCl_3 solutions are dried (MgSO_4) and evaporated to yield the diol.

10.2.3 Typical conditions for the oxidation of alkenes to aldehydes or ketones

Method A: CTMA- MnO_4 (0.4 g, 1 mmol) in CH_2Cl_2 (6 ml) is added to the alkene (1 mmol) in CH_2Cl_2 (7 ml) at 25°C and the mixture is stirred for 2–6 h. Et_2O (50 ml) is added and the mixture is filtered through Celite. The dried (MgSO_4) filtrate is evaporated to yield the carbonyl compounds (>80%).

Method B: KMnO_4 (15.8 g, 0.1 mol) is added over *ca.* 2 h with stirring to the alkene (0.1 mol) in CH_2Cl_2 (100 ml) and a $\text{AcONa}:\text{AcOH}$ buffer (pH 3, 30 ml). Et_2O (500 ml) is added, and the aqueous phase is separated and extracted with Et_2O (3×150 ml). The dried (MgSO_4) ethereal solutions are evaporated to yield the carbonyl compound.

10.2.4 Typical conditions for the oxidation of alkenes to carboxylic acids

Powdered KMnO_4 (1.2 mol) is added portionwise at $<30^\circ\text{C}$ over 2 h to the alkene (0.03 mol) and Aliquat (0.2 g, 0.5 mmol) in CH_2Cl_2 ($n\text{-C}_5\text{H}_{12}$ or PhH) (100 ml) and AcOH (30 ml). The mixture is stirred at room temperature for 12 h and aqueous NaHSO_3 (5%, 100 ml) is then added. The aqueous phase is separated, acidified with concentrated HCl, and the carboxylic acid is collected (if it has precipitated), or the acidic solution is saturated with NaCl and extracted with Et_2O (2×10 ml). Evaporation of the ethereal extracts yields the water-soluble carboxylic acid.

10.2.5 Oxidation of non-terminal alkynes to diketones

The alkyne (9 mmol) and Adogen (1.5 g, 3.4 mmol) in CH_2Cl_2 (100 ml) and AcOH (1 ml) are added to KMnO_4 (alkyne: KMnO_4 ratio 1 : 4 to 1 : 2.7) in H_2O (100 ml) and the mixture is stirred for 6 h under reflux. The mixture is cooled to room temperature and NaHSO_3 (2 g) is added and the mixture stirred for 15 min. The solution is acidified with conc. HCl and the precipitated MnO_2 is reduced with a further addition of NaHSO_3 . The aqueous phase is separated, saturated with NaCl, and extracted with CH_2Cl_2 (3×75 ml). The combined organic solutions are washed with aqueous NaOH (5%, 3×75 ml), dried (MgSO_4), and evaporated to yield the diketone [RCOCOR : R = Ph, 93% (KMnO_4 :alkyne ratio 3 : 1); Ph, $n\text{-Pr}$, 81% (2.7:1); Ph, $n\text{-Bu}$, 41% (4.1 : 1); $n\text{-C}_6\text{H}_{13}$, 54%, (2.7:1); $n\text{-C}_7\text{H}_{15}$, 68% (4.1 : 1)].

The mechanism [26] of the oxidation of non-terminal alkynes by quaternary ammonium permanganates to give vicinal diketones [e. g. 18, 27] has been studied. Normally, terminal alkynes are totally oxidized in acetic acid to carboxylic acids [13, 27, 28] using a procedure analogous to 10.2.4.

Preformed benzyltrithethylammonium permanganate has been employed in stoichiometric amounts in acetic acid for the oxidation of alkanes to give alcohols [26]. Yields tend to be low and have little synthetic value. However, under similar conditions, cathines are oxidized in a one-pot reaction to cathin-6-ones in good yield ($>65\%$) via the initial oxidation of the annular CH_2 to $\text{C}=\text{O}$ and subsequent dehydrogenation of the ring [29]. Alkylarenes are also susceptible to oxidation under phase-transfer catalytic conditions [30–32]; methylene groups are oxidized under basic conditions to ketones in high yield ($>75\%$) and triphenylmethane is oxidized to trityl alcohol (80%) [32]. Methyl groups are oxidized to carboxylic acids and ethyl groups to acetyl or α -acetoxyethyl groups [31]. Consequently, it is inadvisable to use toluene, as the organic phase, for such reactions.

10.2.6 Acetoxybenzoic acids

TEBA- MnO_4 (0.31 g, 1 mmol) and KMnO_4 (1.58 g, 10 mmol) in AcOH (15 ml) are added to the (acetoxyaryl)alkane (5 mmol) in AcOH (5 ml) at 30°C . The mixture is stirred for 3 days and then poured into aqueous Na_2SO_3 (2%, 100 ml). The aqueous solution is extracted with Et_2O (4×60 ml) and the ethereal extracts are further extracted with aqueous NaHCO_3 (2×100 ml). The basic extracts are acidified with H_2SO_4 (5M) to

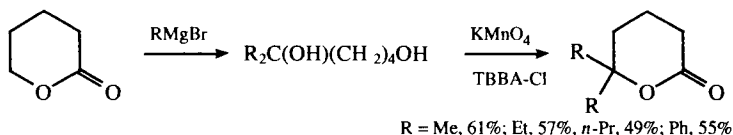
produce the acetoxybenzoic acid. The ethereal solutions contain the non-acidic ester and ketonic products.

10.2.7 Oxidation of non-functionalized benzylic compounds

KMnO₄ (2.37 g, 15 mmol), KOH (0.28 g), and TBA-HSO₄ (0.34 g, 1 mmol) in H₂O (35 ml) are added to the benzylic compound (10 mmol) in CH₂Cl₂ (35 ml) and the mixture is stirred at room temperature until the purple colour disappears (or TLC analysis shows complete oxidation). The mixture is acidified with AcOH (5 ml) and Na₂SO₃ is added until the brown colour disappears. The organic phase is separated, washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the ketone (e.g. PhCOPh, 80%; 2-pyridylCOPh, 75%; 9,10-anthraquinone from 9,10-dihydroanthracene, 90%).

Allyl and aryl ethers produce carboxylic esters in good yields (60–80%) upon oxidation by benzyltriethylammonium permanganate in dichloromethane [33], e.g. dibenzyl ether gives benzyl benzoate (80%).

Primary and secondary alcohols are oxidized slowly at low temperatures by benzyltriethylammonium permanganate in dichloromethane; primary alcohols produce methylene esters (60–70%), resulting from reaction of the initially formed carboxylate anion with the solvent, with minor amounts of the chloromethyl esters and the carboxylic acids. Secondary alcohols are oxidized (75–95%) to ketones [34]; the yields compare favourably with those obtained using potassium permanganate on a solid support. 1,5-Diols are oxidized by potassium permanganate under phase-transfer catalytic conditions to yield δ,δ -disubstituted- δ -valerolactones [35] (Scheme 10.1).



Scheme 10.1

Although potassium permanganate does not oxidize acetals in aqueous media, with a phase-transfer catalyst under non-aqueous conditions, cyclic acetals are converted into hydroxyalkyl carboxylates [36].

10.2.8 Oxidation of alcohols to methylene esters and ketones

The alcohol (5 mmol) and TEBA-MnO₄ (3.1 g, 10 mmol) in CH₂Cl₂ (75 ml) are stirred at room temperature for 1 to 2 days and the mixture is then poured into aqueous Na₂SO₃ (2%, 100 ml) and stirred for a further 30 min at room temperature. The organic layer is separated, washed with NaHCO₃ (sat. soln, 2 × 25 ml) and H₂O (2 × 25 ml), dried (MgSO₄), and evaporated to yield the non-acidic products.

10.2.9 Oxidation of 5,5-disubstituted pentane-1,5-diols

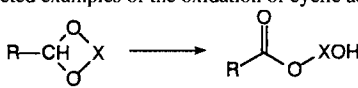
The diol (0.18 mol) is added to KMnO_4 (7.6 g) and TBBA-Cl (0.8 g, 2.4 mmol) in PhH (300 ml) and H_2O (300 ml) and the mixture is stirred at room temperature for 12 h. NaHSO_3 and conc. H_2SO_4 are added to quench the reaction and dissolve the precipitated MnO_2 . The aqueous phase is separated and extracted with Et_2O (3×15 ml). The combined organic solutions are dried (Na_2SO_4) and evaporated to yield the 5,5-disubstituted δ -valerolactone

10.2.10 Oxidation of cyclic acetals (Table 10.2)

The acetal (0.01 mol) in CH_2Cl_2 (20 ml) is added dropwise to KMnO_4 (0.02 mol) in H_2O and TEBA-Cl (1 mmol) in CH_2Cl_2 (20 ml) and the mixture is stirred for 4 h at room temperature. Aqueous NaHSO_3 (20%, 20 ml) is added and the mixture is acidified with conc. HCl. The aqueous phase is separated, saturated with NaCl, and extracted with Et_2O . Na_2CO_3 is added to the combined organic solutions and the solution is filtered, dried (MgSO_4), and evaporated to yield the ester.

TABLE 10.2

Selected examples of the oxidation of cyclic acetals

			% yield of ester
R =	X =		
Ph	$-(\text{CH}_2)_2-$	95	
	$-\text{CH}_2\text{CHMe}-$	91	
	$-(\text{CH}_2)_3-$	85	
<i>n</i> -Bu	$-(\text{CH}_2-)$	73	

One report suggests that there is no particular advantage in using phase-transfer conditions for the permanganate oxidation of sulphides to sulphones [37]. Yields are generally no better than those obtained in the absence of the catalyst and the procedure fails to oxidize 1,3-oxathiolanes [37]. However, other work indicates that the use of a stoichiometric amount of benzyltriethylammonium permanganate in dichloromethane provides a useful route for the conversion of sulphides and sulfoxides into sulphones [38] and, with the exception of the reaction with allylic sulphides which gives a mixture of undefinable products, all conversions proceed rapidly in good yield (Table 10.3).

10.2.11 Conversion of sulphides and sulfoxides into sulphones

The sulphide (or sulfoxide) (5 mmol) in CH_2Cl_2 (50 ml) and AcOH (5 ml) is cooled to -10°C and TEBA- MnO_4 (11 mmol or 5 mmol) is added portionwise with stirring. The mixture is stirred at -10°C and Et_2O (100 ml) is added. The mixture is allowed to stand

TABLE 10.3
Permanganate oxidation of sulphides and sulfoxides

		% yield of sulphone
<i>With sulphides, R¹SR²</i>		
R ¹ = Ph	R ² = <i>n</i> -C ₃ H ₇	85
PhCH ₂	<i>n</i> -C ₃ H ₇	98
EtO ₂ CCH ₂	(CH ₂) ₃ CO ₂ Et	87
PhCOC(Me)H	CH ₂ CO ₂ Me	74
-CH ₂ CO(CH ₂) ₃ -		65
-(<i>o</i> -C ₆ H ₄)NH-(<i>o</i> -C ₆ H ₄)-		72
<i>With sulfoxides, R¹SOR²</i>		
R ¹ = PhCOCH ₂	R ² = Me	92
cyclo-C ₆ H ₁₀ COCH ₂	Me	93
-CH ₂ CO(CH ₂) ₃ -		63

for 30 min and is then filtered. The filtrate is washed with H₂O (2 × 25 ml) and with aqueous NaHCO₃ (sat. soln., 25 ml), dried (MgSO₄), and evaporated to yield the sulphone.

Catalysed oxidation of primary and secondary amines generally has little synthetic value. Primary amines yield either a mixture of nitriles and amides (*ca.* 30%) or, in the case of arylamines, the azo derivatives (42–99%) [39]. Symmetrical and non-symmetrical azoarenes are also produced in good yields (~60%) from the reaction of acetanilides with nitroarenes under basic solid:liquid conditions, although higher yields are obtained using TDA-1 [40].

Secondary amines form amides, but again in relatively low yield (30–45%). In contrast, tertiary amines form *N,N*-disubstituted amides exclusively in high yield [41], e.g. *N,N*-dimethylaniline is oxidized to *N*-methylformanilide (78%), *N,N*-diethylaniline gives *N*-ethylacetanilide (63%) and *N,N*-dimethylbenzylamine gives *N,N*-dimethylbenzamide (72%). This procedure is superior to other conversions of tertiary aromatic amines into amides. In an analogous manner, tertiary benzylamines are converted into benzamides and *N*-benzylcarboxamides under solid:liquid catalytic conditions [42]. The catalytic oxidation of tertiary aliphatic amines with an excess of the permanganate has been used in the conversion of chiral 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*b*]pyridines into the corresponding 3-oxo derivatives, which are readily converted into the chiral 1,4-dihydropyridines [43].

10.2.12 Azoarenes from primary arylamines

KMnO₄ (4.52 g) in H₂O (200 ml) is added with stirring to the aniline (10 mmol) and TBA-Br (0.48 g, 1.5 mmol) in PhH (100 ml) at 20°C (80°C for the less basic amines). The mixture is stirred for 8 h, filtered, and the organic phase is separated, dried (Na₂SO₄), and evaporated to yield the azoarene (e.g. 90% from 2,4,6-Me₃C₆H₂NH₂; 99%, 2,4,6-Ph₃C₆H₂NH₂; 42%, 2,4,6-Cl₃C₆H₂NH₂).

10.2.13 Symmetrical and non-symmetrical azoarenes

The acetanilide (0.1 mol), powdered NaOH (16 g, 0.4 mol), K_2CO_3 (13.8 g, 0.1 mol), and TBA-Br or TEBA-Cl (4 mmol) are stirred in xylene at 100°C for 1 h. The nitroarene (0.1 mol) is added and the mixture is stirred at 130°C for a further 8 h. After hot filtration, the solvent is evaporated and the residue is taken up in petroleum ether and chromatographed on silica to yield the azo compound.

10.2.14 Oxidation of tertiary amines to amides

Method A: The tertiary amine (5 mmol) and TEBA-MnO₄ (3.11 g, 10 mmol) in CH_2Cl_2 (75 ml) are stirred at 0–40°C for 0.5 to 2 days. The mixture is then poured into aqueous Na₂SO₃ (2%, 100 ml) and the mixture is stirred for 30 min at room temperature. The organic layer is separated, washed with dilute HCl (2M, 25 ml), H₂O (2 × 25 ml), NaHCO₃ (sat. soln., 2 × 25 ml) and H₂O (2×25 ml), dried (MgSO₄), and evaporated to yield the amide.

Method B: Powdered KMnO₄ (0.47 g, 3 mmol) is added to the tertiary benzylamine (1 mmol) and TEBA-Cl (0.68 g, 3 mmol) in CH_2Cl_2 (10 ml) and the solution is refluxed for 3 h, then cooled to room temperature, and stirred with aqueous NaHSO₃ (20%, 10 ml). The organic phase is separated, washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the amide.

Secondary nitroalkanes are oxidized by cetyltrimethylammonium permanganate to yield ketones in moderate to good yield [44]. The reaction is sufficiently mild to leave double bonds and hydroxyl groups unaffected.

10.2.15 Conversion of nitroalkanes into carbonyl compounds (Table 10.4)

Et₃N (0.2 g, 2 mmol) in CH_2Cl_2 (2 ml) is stirred with the nitroalkane (2 mmol) in CH_2Cl_2 (15 ml) for 10 min. CTMA-MnO₄ (1.21 g, 3 mmol) in CH_2Cl_2 (5 ml) is then added dropwise over 5 min and the solution is stirred at room temperature for 3–5 h. The solution is reduced to half volume and Et₂O (50 ml) added. The ethereal solution is filtered through Celite, dried (MgSO₄), and evaporated to yield the carbonyl compound.

TABLE 10.4

Selected examples of the conversion of nitroalkanes into carbonyl compounds

Nitroalkane	Product	% yield
<i>n</i> -C ₇ H ₁₅ NO ₂	<i>n</i> -C ₆ H ₁₃ CHO	71
cyclo-C ₆ H ₁₁ NO ₂	cyclohexanone	80
MeCO(CH ₂) ₃ NO ₂	MeCO(CH ₂) ₂ CHO	57
MeCO(CH ₂) ₂ CH(Me)NO ₂	MeCO(CH ₂) ₂ COMe	65
MeCH(OH)(CH ₂) ₂ CH(Me)NO ₂	MeCH(OH)(CH ₂) ₂ COMe	62
CH ₂ =CH(CH ₂) ₈ CH ₂ NO ₂	CH ₂ =CH(CH ₂) ₈ CHO	66
PhCH ₂ NO ₂	PhCHO	89
Ph(CH ₂) ₂ NO ₂	PhCH ₂ CHO	80
PhCH(Me)NO ₂	PhCOMe	87

Trans-oxidative chlorination of alkenes using a benzytriethylammonium permanganate–chlorotrimethylsilane system produces vicinal dichloroalkanes in high yield [45]. The procedure is superior to the earlier described chlorination using benzytriethylammonium permanganate–oxalyl chloride system, which is not stable above -35°C [46, 47]. The chlorination agent is not fully characterized, but is thought to be a trimethylsilyloxymanganese(VII) complex or hypochlorite [45]. Oxiranes ring-open under analogous conditions to yield α -chloroalkanols [45], for example, 2-chloro-2-phenylethanols are obtained from phenyloxiranes. Curiously, it is reported that 1,2-epoxycyclooct-5-ene is converted into the 5,6-dichloro-1,2-epoxycyclooctane (60%) using procedure 10.2.16, whereas a 2-fold amount of the permanganate and chlorotrimethylsilane at 20°C produces 2-chlorocyclooct-5-enol (77%). This contrasts with the reaction using the permanganate–oxalyl chloride system, when the dichlorooxirane is obtained at -70°C , but an excess of oxalyl chloride leads to 2,5,6-trichlorocyclooctanol [47].

10.2.16 Oxidative chlorination of alkenes

TEBA-Cl (0.64 g, 2.8 mmol) is added to KMnO_4 (0.45 g, 2.8 mmol) in CH_2Cl_2 (17 ml) at 20°C . The mixture is stirred for 45 min and then cooled to 0°C and Me_3SiCl (1.22 g, 11.24 mmol) is added dropwise, followed by the alkene (2.8 mmol) in CH_2Cl_2 (3 ml). The mixture is allowed to come to 20°C and is stirred for *ca.* 40 min. The organic solution is washed well with aqueous $\text{Na}_2\text{S}_2\text{O}_3$, dried (MgSO_4), and evaporated to yield the *vic*-dichloroalkane (e.g. 95% from *trans*-stilbene; 94% from *trans*-oct-5-ene; 81% from *cis*-oct-5-ene; 84% from *trans*-oct-2-ene; 86% from hept-1-ene).

Sulphides are oxidized by the permanganate–chlorotrimethylsilane system at -15°C to sulfoxides (80%) [45].

Although permanganate ions are not generally used to effect oxidative coupling of phenols, it has been shown that, in the presence of a catalyst in an organic solvent, 2-methoxyphenols are coupled oxidatively under very mild conditions to produce the dimeric products (>50%) [48]. Unsaturated substituents are not oxidized under the mild conditions.

10.2.17 Oxidative coupling of 2-methoxyphenols

TBMA- MnO_4 (0.48 g, 1.5 mmol) in CH_2Cl_2 (10 ml) is added at 0°C to the phenol (3 mmol) in CH_2Cl_2 (5 ml) under N_2 . After 15 min, H_2O (10 ml) is added and the excess permanganate is destroyed with SO_2 . The organic phase is separated, washed with aqueous HCl (0.1 M, 3×5 ml), dried (MgSO_4), and evaporated to yield the crude dimeric product, which is purified by flash chromatography on silica.

Triazolines have been aromatized in good yield under two-phase conditions using potassium permanganate in the presence of tetra-*n*-butylammonium chloride [49].

10.2.18 Conversion of 1H-4,5-dihydro-1,2,3-triazoles into 1,2,3-triazoles

The triazoline (2 mmol) in PhH (50 ml) is refluxed with KMnO_4 (1.58 g, 10 mmol) in water (100 ml) containing TBA-Cl (28 mg, 0.125 mmol). The aqueous phase is separated and extracted with CH_2Cl_2 (3×20 ml). The combined organic solutions are washed well with aqueous Na_2SO_3 and H_2O , dried (MgSO_4), and evaporated to yield the triazole (e.g. 1-subst., 5-subst., reaction time, yield: Ph, 4-pyridyl, 2 h, 65%; 4- $\text{CH}_3\text{C}_6\text{H}_4$, 4-pyridyl, 2 h, 73%; 4- ClC_6H_4 , 4-pyridyl, 3 h, 72%; Ph, 2-quinoliny, 7 h, 40%; 4- $\text{O}_2\text{NC}_6\text{H}_4$, 4- $\text{O}_2\text{NC}_6\text{H}_4$, 8 h, 38%).

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10.3 CHROMATE AND DICHROMATE MEDIATED OXIDATIONS

The transfer of the dichromate anion from aqueous solution into an organic phase was first achieved by the addition of arsonium salts [1] and a similar transfer can be effected by many quaternary ammonium salts, although the nature of the transferred anion has not been fully established and it depends on the pH of the aqueous phase [2–4]. The transfer of the dichromate anion from a basic aqueous phase is negligible and, although Adogen and tetra-*n*-butylammonium salts transfer ‘dichromate’ anions efficiently into an organic phase from neutral aqueous media [2], the addition of acid enhances the transfer process. Under the acidic conditions, it is probable that it is the HCrO_4^- ion which migrates [3]. A solid ammonium salt, thought to be $(n\text{-Bu}_4\text{N}^+)_2\text{Cr}_2\text{O}_7^-$, has been obtained by the addition of tetra-*n*-butylammonium hydrogen sulphate to aqueous potassium dichromate [5, 6]. As with the solid ammonium permanganates, this compound is EXTREMELY UNSTABLE.

10.3.1 Tetra-*n*-butylammonium dichromate

$\text{K}_2\text{Cr}_2\text{O}_7$ (48.5 g, 0.25 mol) in H_2O (100 ml) is added portionwise over 2 h to TBA- HSO_4 (34.0 g, 0.1 mol) in CH_2Cl_2 (100 ml) at room temperature. The ammonium dichromate salt (97%) m.p. 129–133°C precipitates out and is washed with H_2O and dried under vacuum.

It has been claimed that chromium trioxide reacts with tetra-*n*-butylammonium chloride in water to produce tetra-*n*-butylammonium chromate, $n\text{-Bu}_4\text{N}^+\text{HCrO}_4^-$ [7], whereas benzyltriethylammonium dichromate is obtained from the closely analogous reaction of benzyltriethylammonium chloride with chromium trioxide in dilute hydrochloric acid [8].

Chromium trioxide is also solublized in dichloromethane in the form of complex chromates $\text{Q}^+[\text{X}(\text{CrO}_3)_n]^-$ by the addition of an appropriate tetra-*n*-butylammonium salt [9–14].

10.3.2 'Tetra-*n*-butylammonium chromate'

CrO₃ (1.0 g, 10 mmol) in H₂O (25 ml) is stirred with TBA-Cl (2.92 g, 10.5 mmol) in H₂O (50 ml) at room temperature. The mixture is cooled to 0°C and the yellow precipitate (77%) is collected, washed with H₂O, and dried over P₂O₅ under vacuum.

10.3.3 Benzyltriethylammonium dichromate

CrO₃ (10 g, 0.1 mol) in HCl (3 M, 200 ml) is added to TEBA-Cl (22.7 g, 0.1 mmol) in H₂O (250 ml). The crude product is recrystallized from aqueous MeCOMe to give the analytically pure (TEBA)₂-Cr₂O₇ (86%), m.p. 89°C.

10.3.4 Tetra-*n*-butylammonium chlorochromate TBA-ClCrO₃ and benzyltrimethylammonium chlorochromate TMBA-ClCrO₃

Method A: TBA-Cl (0.278 g, 1 mmol) is added with stirring to CrO₃ (0.1 g, 1.0 mmol) in CH₂Cl₂ (5 ml) at room temperature. After complete dissolution of the oxide, EtOAc (5 ml) and *n*-C₆H₁₄ (100 ml) are added. TBA-ClCrO₃ (80%) m.p. 184–185°C crystallizes from the solution.

Method B: CrO₃ (5.0 g, 50 mmol) in HCl (6 M, 10 ml) is stirred at 0°C for 5 min. TMBA-OH (40% in H₂O, 23 g, 55 mmol), or TBA-HSO₄ (16.95 g, 50 mmol) in HCl (6M, 20 ml), is added over 10 min. The precipitated ammonium salt is collected, washed with aqueous HCl (6M, 50 ml) and H₂O (2 × 10 ml), and dried under vacuum [TMBA-ClCrO₃ (96%), m.p. 85°C (decomp.); TBA-ClCrO₃ (80%)].

Generally, catalysed oxidations using dichromate from neutral aqueous solutions are slow. Primary and secondary alcohols are oxidized selectively at 55°C slowly over a period of 15–24 hours to yield the corresponding aldehydes and ketones and the addition of sulphuric acid enhances the rate of the reaction without causing over-oxidation to the carboxylic acids [2–8, 15, 16]. The yields from low molecular weight aliphatic primary alcohols are usually very poor, owing to the greater solubility of the aldehyde in the aqueous phase and subsequent oxidation to the carboxylic acid. Unsaturation in the substrate results in higher yields of the aldehyde or ketone without oxidation of the double bonds.

A *cis*-diol function of triols can be protected as its dioxolane derivative and subsequent oxidation produces the monocarbonyl compound without cleavage of the dioxolane ring [15]. Secondary hydroxyl groups can be oxidized selectively by the initial protection of the primary groups by silylation, for example, *t*-butyldimethylsilyl ethers are stable to oxidation by the complex chlorochromate allowing the oxidation of secondary hydroxyl groups into the ketones in good yield [13]. Hydroxyl groups can also be protected during oxidation by conversion into their tetrahydropyranyl derivatives [15].

Haloalkanes are readily oxidized to the corresponding aldehydes or ketones. The best yields are attained with secondary alcohols and unsaturated hydroxyl groups [5].

α-Nitroketones, which are valuable intermediates in organic synthesis, are

obtained in high yield under mild conditions from the α -nitroalkanols using potassium dichromate or chromate in the presence of tetra-*n*-butylammonium hydrogen sulphate [17]. The nitroketones have also been obtained in a catalytic one-pot reaction from the aldehyde and nitroalkane.

The complex chromium salts [9–14] have a reactivity and selectivity comparable with that of pyridinium chlorochromate. Used at a catalytic level, the salts are more efficient than when stoichiometric amounts are used. The best results are obtained under solid:liquid conditions (10.3.5.F, when $X = \text{HSO}_4^-$ or F^-); good conversions are also obtained with triflates and tosylates. Surprisingly, although relatively efficient under solid:liquid conditions, poorer conversions usually result from the use of the chloride and bromide salts under liquid:liquid two-phase conditions.

An effective oxidation of α,β -unsaturated primary alcohols and benzylic alcohols, but not saturated alcohols, to the corresponding aldehydes has been achieved using polymer-supported quaternary ammonium dichromate [14].

10.3.5 Oxidation of primary and secondary alcohols (Tables 10.5 and 10.6)

Method A: $\text{K}_2\text{Cr}_2\text{O}_7$ (19.4 g, 66 mmol) in H_2SO_4 (30%, 120 ml) is added at -5 to 0°C to the alcohol (0.1 mol) and TBA- HSO_4 (3.4 g, 0.01 mol) in CH_2Cl_2 (200 ml) over 1 h. The mixture is stirred at -5°C and aqueous FeSO_4 (10%, 100 ml) is then added. The organic phase is separated, washed with aqueous NaOH (10%, 50 ml) and H_2O (50 ml), dried (MgSO_4), and evaporated to yield the carbonyl compound.

Method B: $(\text{TEBA})_2\text{-Cr}_2\text{O}_7$ (245 g, 35 mmol) and the alcohol (50 mmol) in HMPT (50 ml) are heated at 60 – 80°C over 4–6 h. When the conversion is complete, as indicated by TLC, HCl (0.1 M, 200 ml) is added. The aqueous mixture is extracted with Et_2O (4×50 ml) and the ethereal extracts are dried (MgSO_4) and evaporated to yield the carbonyl compound.

Method C: The alcohol (10 ml) and TBA- HSO_4 (0.3 g, 0.9 mmol) in CH_2Cl_2 (25 ml) are shaken with $\text{K}_2\text{Cr}_2\text{O}_7$ (0.97 g, 3.3 mmol) in H_2SO_4 (9 M, 25 ml). The organic phase is separated, washed with H_2O (2×15 ml), dried (MgSO_4), and evaporated to yield the carbonyl compound.

Method D: $\text{Na}_2\text{Cr}_2\text{O}_7$ (0.86 g, 3.3 mmol) in aqueous H_2SO_4 (3M, 25 ml) is added to the alcohol (10 mmol) and TBA- HSO_4 (0.34 g, 1.0 mmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (25 ml). The mixture is stirred at room temperature and then the organic phase is separated, dried (Na_2SO_4), and evaporated to yield the carbonyl compound.

Method E: The alcohol (2.52 mmol) in CHCl_3 (10 ml) is added with stirring to TBA- HCrO_4 (2.17 g, 6.04 mmol) at room temperature. The mixture is heated at 60°C for ca. 2–4 h and then diluted with Et_2O (25 ml). The organic solution is poured into aqueous NaOH (1M, 50 ml), separated, washed well with saturated brine, dried (Na_2SO_4), and evaporated to yield the carbonyl compound.

Method F: The alcohol (1 mmol) in CH_2Cl_2 (1 ml) is added dropwise to CrO_3 (0.15 g, 1.5 mmol) and the ammonium salt TBA-X (0.075 mmol) in CH_2Cl_2 (2 ml). When the reaction is complete, as shown by TLC analysis, the mixture is filtered through Celite and evaporated. The residue is triturated with Et_2O and the ethereal extracts are evaporated to yield the carbonyl compound.

TABLE 10.5
Selected examples of the oxidation of alcohols to aldehydes and ketones

R ¹ R ² CHOH		% yield R ¹ COR ²				
		10.3.5.A	10.3.5.B	10.3.5.C	10.3.5.D	10.3.5.E
R ¹ = Me	R ² = H	—	—	5	45	—
Et	H	19	—	—	—	—
<i>n</i> -C ₃ H ₇	H	—	—	34	97	—
<i>n</i> -C ₅ H ₁₁	H	90	—	—	—	—
<i>n</i> -C ₇ H ₁₅	H	91	30	—	95	—
<i>n</i> -C ₈ H ₁₇	H	—	—	82	—	—
<i>n</i> -C ₁₁ H ₂₃	H	98	—	—	—	—
<i>n</i> -C ₁₅ H ₃₁	H	98	—	—	—	—
<i>n</i> -C ₁₆ H ₃₃	H	—	—	90	—	—
2-pyranylo(CH ₂) ₇	H	83	—	—	—	—
HC(OCMe ₂ OCH ₂)(CH ₂) ₃	H	10	—	—	—	—
HC(OCMe ₂ OCH ₂)(CH ₂) ₈	H	78	—	—	—	—
CH ₂ =CH(CH ₂) ₉	H	—	—	95	—	—
Ph	H	—	90	92	100	81 (1 h)
4-MeOC ₆ H ₄	H	98	97	80	93	—
2,4,5-MeO ₃ C ₆ H ₂	H	—	—	—	—	75 (3 h)
4-ClC ₆ H ₄	H	—	—	85	92	—
4-MeC ₆ H ₄	H	—	—	95	—	—
4-O ₂ NC ₆ H ₄	H	—	—	84	—	—
2-furyl	H	—	71	—	—	—
2-pyridyl	H	—	—	—	—	43 (3 h)
PhCH ₂	H	—	—	62 ^a	—	—
Ph(CH ₂) ₂	H	—	—	80	85	—
<i>n</i> -C ₆ H ₁₃	Me	95	—	95	—	—
-(CH ₂) ₅ -	—	—	30	65	88	—
Ph	Me	—	—	80	—	—
Ph	CO ₂ Et	—	—	96	—	—
Ph	Ph	—	99	—	—	91 (3 h)
4-MeOC ₆ H ₄	Ph	—	95	—	—	—
PhCH=CH	H	—	—	80	—	—
PhCH=CH	Me	—	—	—	—	88 (4 h)
PhCH=CH	Ph	—	—	—	—	92 (4 h)
PhCH=CHCH ₂ OH	—	80	90	0	39	90 (3.5 h)
Nerol	—	—	—	—	71	86 (3 h)
Geraniol	—	—	—	—	—	83 (3 h)

^a 91% with 4.1 mol of K₂Cr₂O₇.

10.3.6 Oxidation of haloalkanes (Table 10.7)

The haloalkane (0.01 mol) and (TBA)₂-Cr₂O₇ (4.7 g, 66 mmol) in CHCl₃ (17.5 ml) are heated under reflux for 3 h. The solution is filtered through silica (20 g) and the silica is washed with Et₂O (100 ml). The combined organic solutions are dried (MgSO₄) and evaporated to yield the carbonyl compound.

TABLE 10.6

Selected examples of the oxidation of alcohols to aldehydes and ketones using complex salts from CrO_3 and $n\text{-Bu}_4\text{N}^+\text{X}^-$

Alcohol	X	Reaction time ^a	Product	% yield
$n\text{-C}_8\text{H}_{17}\text{OH}$	Cl	5 min	$n\text{-C}_7\text{H}_{15}\text{CHO}$	70
$n\text{-C}_{12}\text{H}_{23}\text{OH}$	Cl	30 h	$n\text{-C}_{11}\text{H}_{23}\text{CHO}$	68 ^b
$n\text{-C}_6\text{H}_{13}\text{CH}(\text{OH})\text{Me}$	HSO_4	20 min	$n\text{-C}_6\text{H}_{13}\text{COMe}$	99 ^c
PhCH_2OH	Cl	20 min	PhCHO	78
$4\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OH}$	Cl	7 h	$4\text{-MeOC}_6\text{H}_4\text{CHO}$	85 ^d
$4\text{-ClC}_6\text{H}_4\text{CH}_2\text{OH}$	Cl	8 h	$4\text{-ClC}_6\text{H}_4\text{CHO}$	78 ^d
$4\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{OH}$	Cl	4 min	$4\text{-O}_2\text{NC}_6\text{H}_4\text{CHO}$	80 ^d
$2\text{-MeOC}_6\text{H}_4\text{CH}_2\text{OH}$	Cl	8 min	$2\text{-MeOC}_6\text{H}_4\text{CHO}$	87 ^d
$\text{PhCH}=\text{CHCH}_2\text{OH}$	Cl	15 min	$\text{PhCH}=\text{CHCHO}$	85
cyclo- $\text{C}_6\text{H}_{11}\text{OH}$	Cl	20 min	cyclohexanone	99
cyclo- $\text{C}_{12}\text{H}_{23}\text{OH}$	Cl	30 min	cyclododecanone	58 ^e
cyclohex-2-enol	Cl	24 h	cyclohex-2-enone	90
$\text{PhCH}(\text{OH})\text{Me}$	Cl	2 min	PhCOMe	82 ^d
$\text{PhCH}(\text{OH})\text{Ph}$	Cl	1 h	PhCOPh	82 ^d
Geraniol	Cl	24 h	Geranial	87 ^{f,g}
Carveol	Cl	2 h	Carvone	58 ^h

^a Using procedure 10.3.5.F. ^b 97% using TMBA- ClCrO_3 . ^c 3 : 1 ratio of $\text{K}_2\text{Cr}_2\text{O}_7$:alcohol. ^d 60% yield after 90 min. ^e 97% using TMBA- ClCrO_3 . ^f Nerol produces 95% neral under the same conditions. ^g 83% using TMBA- ClCrO_3 . ^h 83% using TMBA- ClCrO_3 .

TABLE 10.7

Oxidation of halogenoalkanes

Haloalkane	Reaction time	Product	% yield
$n\text{-C}_8\text{H}_{17}\text{Br}$	4 h	$n\text{-C}_7\text{H}_{15}\text{CHO}$	17 ^a
$n\text{-C}_6\text{H}_{13}\text{CH}(\text{Br})\text{Me}$	8.5 h	$n\text{-C}_6\text{H}_{13}\text{COMe}$	72 ^b
PhCH_2Cl	7 h	PhCHO	81
PhCH_2Br	5 min	PhCHO	95
Farnesyl bromide	40 min	Farnesaldehyde	92

^a + 5% unreacted $n\text{-C}_8\text{H}_{17}\text{Br}$, 20% $n\text{-C}_8\text{H}_{17}\text{OH}$, 30% $n\text{-C}_8\text{H}_{17}\text{CO}_2\text{C}_8\text{H}_{17}$. ^b + 19% octenes.

10.3.7 Oxidation of 2-nitroalkanols (Table 10.8)

$\text{K}_2\text{Cr}_2\text{O}_7$ (19.12 g, 65 mmol) in H_2SO_4 (30%, 60 ml) is added at -10°C to the nitroalkanol (0.05 mol) and TBA- HSO_4 (1.7 g, 5 mmol) in CH_2Cl_2 (90 ml). The mixture is stirred for 2 h at -10°C and FeSO_4 (10%, 50 ml) is then added. The organic phase is separated, dried (Na_2SO_4), and evaporated to yield the 2-nitroketone (80–90%).

Aromatic and aliphatic thiols are oxidized by quaternary ammonium dichromate salts to disulphides [8, 13]. Yields are very good, even with the oxidative dimerization of diethyl phosphorothiolothionate to the corresponding disulphide (79%).

TABLE 10.8

Selected examples of the oxidation of 2-nitroalkanol to 2-nitroketones

$R^1CH(OH)C(NO_2)R^2R^3$			% yield of $R^1COC(NO_2)R^2R^3$
$R^1 =$ Me	$R^2 =$ Et	$R^3 =$ H	83 ^a
<i>i</i> -Pr	Et	H	70
<i>n</i> -C ₆ H ₁₃	Et	H	83
CH ₂ =CH(CH ₂) ₂	Me	Me	77
CH ₂ =CH(CH ₂) ₂	Me	H	84
Ph(CH ₂) ₂	Me	H	93
<i>n</i> -C ₆ H ₁₃	H	MeCO(CH ₂) ₂	85 ^b
<i>n</i> -C ₆ H ₁₃	H	MeC(OCH ₂ CH ₂ O)CH ₂	95
Ph(CH ₂) ₂	H	MeC(OCH ₂ CH ₂ O)CH ₂	71 ^b

^a 68% using K₂CrO₄. ^b Using K₂CrO₄.

10.3.8 Oxidative dimerization of thiols to disulphides

(TBA)₂-Cr₂O₇ (0.63 g, 0.9 mmol) or TBA-ClCrO₃ (1.9 g, 5 mmol) in CH₂Cl₂ (10 ml) is added to the thiol (20 mmol) in CH₂Cl₂ (5 ml) at 0–5°C under N₂. The reaction mixture is stirred for 1 h and the solvent is then removed under reduced pressure. The residue is taken up in dilute HCl (2M, 30 ml) and the acidic solution is extracted with Et₂O (4 × 15 ml). The ethereal extracts are dried (MgSO₄) and evaporated to yield the disulphide. (*n*-BuS)₂ 82%; (PhCH₂S)₂ 87%; (PhS)₂ 87%; (4-MeC₆H₄S)₂ 100%; (4-MeOC₆H₄S)₂ 90%; (4-ClC₆H₄S)₂ 92%.

Arenes which are susceptible to oxidation are converted into the quinones under relatively mild conditions using a quaternary ammonium dichromate salt in sulphuric acid. The molarity of the acid is crucial for the success of the reaction. In dilute acid, virtually no oxidation takes place. Optimum conditions appear to require 10 M sulphuric acid and an excess of potassium dichromate.

10.3.9 Conversion of arenes into quinones

The arene (10 mmol) in ClCH₂CH₂Cl (25 ml) is stirred with an excess of K₂Cr₂O₇ (13.5 or 20 mmol) and TBA-HSO₄ (0.34 g, 1 mmol) in H₂SO₄ (10 M, 25 ml) for 2–5 min. The mixture is poured into H₂O (50 ml) and the organic phase is separated, washed with aqueous NaHCO₃ (sat. soln 2 × 25 ml) and H₂O (2 × 25 ml), dried (MgSO₄), and evaporated to yield the quinone [e.g. anthraquinone 92% (13.5 mmol of K₂Cr₂O₇; 2 min at 70°C); naphthaquinone 39% (20 mmol K₂Cr₂O₇; 5 min at 25°C); 2-methyl-1,4-naphthaquinone 56% (20 mmol K₂Cr₂O₇; 5 min at 25°C)].

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10.4 OXIDATION USING HYPOCHLORITE AND CHLORITE ANIONS

The scope and mechanism of the hypochlorite oxidation under phase-transfer conditions have been reviewed [1, 2]. The technique is extremely effective for the conversion of carbinols into aldehydes or ketones (Table 10.9) [1, 2]. The high yielding oxidation of secondary alcohols is particularly facile when ethyl acetate is used as the organic phase [3] but, as primary aliphatic alcohols are oxidized less readily than aldehydes, they frequently undergo further oxidation to the carboxylic acids [1, 2]. Moderation of the reactivity of hypochlorite by the addition of the free radical, 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO), reduces further oxidation of aldehydes to carboxylic acids, and preferentially oxidizes primary hydroxy groups in the presence of secondary hydroxy groups [4], for example, oxidation of a 1 : 1 mixture of decan-1-ol and decan-5-ol produces decanal (99%) and unchanged decan-5-ol (99.8%). Diols produce either cyclic ethers or hydroxy aldehydes, depending on the separation of the hydroxyl groups; 1,2-diols are converted into 1,4-dioxanes [4].

TABLE 10.9
Selected examples of the oxidation of primary and secondary alcohols

Alcohol	Reaction conditions	% recovered alcohol	% yield carbonyl compound
PhCH ₂ OH	CH ₂ Cl ₂ /1.25 h	23	76
4-MeC ₆ H ₄ CH ₂ OH	CH ₂ Cl ₂ /1.25 h	18	78
	EtOAc/30 min	0	100
4-MeOC ₆ H ₄ CH ₂ OH	CH ₂ Cl ₂ /1.25 h	11	79
	EtOAc/30 min	1	92
2-MeOC ₆ H ₄ CH ₂ OH	CH ₂ Cl ₂ /1.5 h	51	41
	EtOAc/1.25 h	2	94
9-Fluorenol	CH ₂ Cl ₂ /35 min	5	92
Benzhydrol	CH ₂ Cl ₂ /2.5 h	16	82
cyclo-C ₇ H ₁₃ OH	CH ₂ Cl ₂ /1 h	3	89
4- <i>t</i> -Bu-cyclo-C ₆ H ₁₀ OH	CH ₂ Cl ₂ /1.25 h	36	39
(23% <i>cis</i> , 77% <i>trans</i>)		(19% <i>cis</i> , 17% <i>trans</i>)	
2-Norbonanol	CH ₂ Cl ₂ /1.25 h	3	89

TABLE 10.10
Oxidation of primary alcohols by hypochlorite moderated by TEMPO

Hydroxy compound	Product	% yield
$n\text{-C}_{11}\text{H}_{23}\text{OH}$	$n\text{-C}_{10}\text{H}_{21}\text{CHO}$	100
$\text{Ph}(\text{CH}_2)_2\text{OH}$	PhCH_2CHO	87 ^a
$\text{THP}(\text{CH}_2)_{10}\text{OH}$	$\text{THP}(\text{CH}_2)_9\text{CHO}$	79
$n\text{-C}_6\text{H}_{13}\text{S}(\text{CH}_2)_2\text{OH}$	$n\text{-C}_6\text{H}_{13}\text{SO}(\text{CH}_2)_2\text{OH}$	90
$\text{RCH}(\text{OH})\text{CH}_2\text{OH}$	2,5-Dialkyl-3,6-dihydroxy-1,4-dioxane	
	$\text{R} = n\text{-C}_{12}\text{H}_{25}$	71
	$\text{R} = n\text{-C}_{10}\text{H}_{21}\text{OCH}_2$	69
$\text{MeCH}(\text{OH})(\text{CH}_2)_3\text{OH}$	2-Hydroxy-5-methyltetrahydrofuran	43
$\text{MeCH}(\text{OH})(\text{CH}_2)_9\text{OH}$	$\text{MeCHOH}(\text{CH}_2)_8\text{CHO}$	58 ^b
$\text{R}^1\text{CH}(\text{OH})\text{CHR}^2\text{CH}_2\text{OH}$	$\text{R}^1\text{CHOHCHR}^2\text{CHO}$	
	$\text{R}^1 = \text{Me}; \text{R}^2 = n\text{-C}_6\text{H}_{13}$	96
	$\text{R}^1 = n\text{-C}_5\text{H}_{11}, \text{R}^2 = n\text{-Bu}$	76

^a + 13% acid. ^b + 15% $\text{MeCO}(\text{CH}_2)_8\text{CHO}$.

10.4.1 Oxidation of alcohols

Method A: Aqueous NaOCl (10%, 50 ml, 0.079 mol) is added to the alcohol (0.01 mol) and TBA-HSO_4 or TBA-Br (0.5 mmol) in CH_2Cl_2 or EtOAc (25 ml) at room temperature and the reaction is monitored by GLC. On completion, the aqueous phase is separated and extracted with CH_2Cl_2 or EtOAc (2×75 ml). The combined organic solutions are dried (MgSO_4) and evaporated to yield the aldehyde or ketone.

Method B with added TEMPO: The alcohol (3 mmol) in CH_2Cl_2 (8 ml) is mixed with KBr (30 mg), TBA-Cl (39 mg, 14 mmol) and TEMPO (4.5 g, 28 mmol) in aqueous NaHCO_3 (sat. soln, 5 ml). The mixture is cooled to 0°C and a mixture of aqueous NaOCl (1.95M, 2 ml), aqueous NaHCO_3 (sat. soln, 3 ml) and brine (6 ml) is added dropwise over 45 min. The mixture is then stirred for 1 h at 0°C and a further 20 min at 20°C . The aqueous phase is separated and extracted with CH_2Cl_2 (3×10 ml). The combined organic solutions are washed with NaHCO_3 (sat. soln, 10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated to yield the product (Table 10.10).

Methylbenzenes are oxidized to the corresponding benzoic acids in very high yield under phase-transfer catalytic conditions by sodium hypochlorite in the presence of ruthenium trichloride, which is initially oxidized to ruthenium tetroxide [5]. Absence of either the ruthenium or the quaternary ammonium salt totally inhibits the reaction.

10.4.2 Oxidation of methylbenzenes to benzoic acids

The methylbenzene (0.1 mol) is added to aqueous NaOCl (3M, 150 ml), TBA-Br (1.6 g, 5 mmol) and $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (0.26 g, 1 mmol) in CH_2Cl_2 (50 ml) and the pH is adjusted to ca. 9.0 by the addition of aqueous H_2SO_4 (20%). The mixture is stirred at 25°C for ca. 8 h while the pH is maintained at ca. 9.0 by the addition of aqueous NaOH (20%). On completion of the reaction, aqueous NaOCl (3 M, ca. 0.5 ml) is added to dissolve any

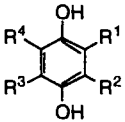
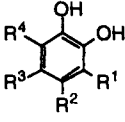
precipitated RuO_2 , and the aqueous phase is separated and acidified with aqueous H_2SO_4 (20%) to precipitate the benzoic acid, $\text{RC}_6\text{H}_4\text{CO}_2\text{H}$ (e.g. $\text{R} = \text{H}$, 92%; 2- NO_2 , 95%; 3- NO_2 , 93%; 4- NO_2 , 94%; 4-MeO, 99%; 4-Cl, 98%; 4-Br, 95%).

Hydroquinones and catechols are oxidized efficiently and cheaply to the corresponding quinones, although it is important to adjust the acidity of the reaction mixture to pH 8, in order to avoid side reactions [6]. Yields tend to be higher when chloroform is used as the solvent.

10.4.3 Oxidation of quinols to quinones (Table 10.11)

The acidity of aqueous NaOCl (10%, 50 ml, 80 mmol) containing TBA- HSO_4 (0.2 g, 0.59 mmol) is adjusted to pH 8 with conc. HCl and then added with stirring to the phenolic compound (18 mmol) in CHCl_3 or EtOAc (50 ml). The mixture is stirred until

TABLE 10.11
Selected examples of quinones from hydroquinones and catechols

				Reaction conditions	% yield of quinone
$\text{R}^1 = \text{H}$	$\text{R}^2 = \text{H}$	$\text{R}^3 = \text{H}$	$\text{R}^4 = \text{H}$	10.4.3/ CHCl_3 /25 min	14
Me	H	H	H	10.4.3/ CHCl_3 /10 min	72
				10.4.3/ EtOAc /10 min	46
<i>t</i> -Bu	H	H	H	10.4.3/ CHCl_3 /10 min	88
				10.4.3/ EtOAc /10 min	67
Ph	H	H	H	10.4.3/ CHCl_3 /10 min	82
				10.4.3/ EtOAc /10 min	42
4-MeC ₆ H ₄	H	H	H	10.4.3/ CHCl_3 /10 min	82
				10.4.3/ EtOAc /10 min	67
H	<i>t</i> -Bu	H	<i>t</i> -Bu	10.4.3/ CHCl_3 /5 min	76
				10.4.3/ EtOAc /5 min	74
$-(o\text{-C}_6\text{H}_4)-$		H	H	10.4.3/ CHCl_3 /15 min	70
				10.4.3/ EtOAc /10 min	51
Me	Me	Me	H	10.4.3/ CHCl_3 /20 min	90
				10.4.3/ EtOAc /20 min	90
Me	Me	Me	Me	10.4.3/ CHCl_3 /10 min	91
				10.4.3/ EtOAc /10 min	85
					
$\text{R}^1 = \text{H}$	$\text{R}^2 = \textit{t}\text{-Bu}$	$\text{R}^3 = \text{H}$	$\text{R}^4 = \text{H}$	10.4.3/ CHCl_3 /10 min	92
H	<i>t</i> -Bu	H	<i>t</i> -Bu	10.4.3/ CHCl_3 /10 min	91

the phenolic compound is consumed, as indicated by TLC analysis, and the organic phase is then separated, washed with H_2O (3×60 ml), dried (MgSO_4), and evaporated to yield the quinone.

Many examples of the phase-transfer catalysed epoxidation of α,β -unsaturated carbonyl compounds using sodium hypochlorite have been reported [e.g. 7–10]. The addition of transition metal complexes also aids the reaction [11], but advantages in reaction time or yields are relatively insignificant, whereas the use of hexaethylguanidinium chloride, instead of a tetra-alkylammonium salt, enhances the rate of epoxidation while retaining the high yields (>95%) [10]. Intermediate β -haloalkanols are readily converted into the oxiranes under basic conditions in the presence of benzyltriethylammonium chloride [12].

Polycyclic arenes having a high degree of bond fixation undergo epoxidation when exposed to tetra-alkylammonium hypochlorites over a pH range of *ca.* 8–9 [13]; phenanthridine is oxidized to phenanthridine.

10.4.4 Epoxidation of alkenes

The alkene (3 mmol) in CH_2Cl_2 (5 ml) is added to the catalyst (0.03 mmol) in aqueous NaOCl (10%, 10.7 ml) and the mixture is stirred at room temperature until the reaction is complete, as shown by TLC analysis. The organic phase is separated, washed well with H_2O , dried (Na_2SO_4), and evaporated to yield the oxirane.

10.4.5 Epoxidation of arenes

The arene (5 mmol) in CHCl_3 (100 ml) is added to aqueous NaOCl (0.6 M, 250 ml) and the pH is adjusted to 8–9 by the addition of conc. HCl . TBA-HSO_4 (0.34 g, 1 mmol) is added and the mixture is stirred until TLC analysis shows complete conversion of the arene. The organic phase is separated, washed well with H_2O , dried (K_2CO_3), and evaporated to yield the epoxide (e.g. 90% from phenanthrene, 76% from 1,2-benzanthracene, 70% from acenaphthene, 19% 2,3:4,5-bis-epoxide from naphthalene).

Catalysed oxidation of non-activated haloalkanes by hypochlorite provides an attractive low-cost and convenient procedure for their conversion into carbonyl compounds [6]; primary haloalkanes produce carboxylic acids and secondary haloalkanes are converted into ketones (Table 10.12). Secondary amines are oxidized to ketones under analogous conditions, whereas primary amines yield nitriles (Table 10.13) [1, 2]. *o*-Nitroanilines are oxidized to benzofurazan-1-oxides [15].

10.4.6 Oxidation of haloalkanes

The haloalkane (2.5 mmol) in MeCN (5 ml) is stirred with aqueous NaOCl (8%, 15 ml) and TBA-HSO_4 (85 mg, 0.25 mmol) at room temperature for 7–24 h until the halide has been consumed. H_2O (35 ml) and Et_2O (25 ml) are added and the organic phase is separated, washed with H_2O (2×10 ml), dried (MgSO_4), and evaporated to yield the oxidation products.

TABLE 10.12

Selected examples of the oxidation of primary and secondary haloalkanes to carboxylic acids and ketones

Haloalkane	% yield	Haloalkane	% yield
<i>Carboxylic acids</i>		<i>Ketones</i>	
4-O ₂ NC ₆ H ₄ CH ₂ Br	94	Ph ₂ CHCl	89
4-O ₂ NC ₆ H ₄ CH ₂ Cl	52	Ph ₂ CHBr	90
2-O ₂ NC ₆ H ₄ CH ₂ Cl	6	9-Bromofluorene	87
4-BrC ₆ H ₄ CH ₂ Br	75		
4-ClC ₆ H ₄ CH ₂ Cl	14 ^a		
3-MeOC ₆ H ₄ CH ₂ Cl	12 ^b		

^a + 6% aldehyde and 34% benzyl alcohol. ^b + 12% aldehyde and 12% benzyl alcohol.

TABLE 10.13

Selected examples of the oxidation of primary and secondary amines

Amine	Reaction conditions	% yield of product
<i>Ketones</i>		
cyclo-C ₆ H ₁₁ NH ₂	10.4.7/2 h	98
Norbornylamine	10.4.7/1.5 h	84
Benzhydrylamine	10.4.7/2 h	94
PhCH(NH ₂)Me	10.4.7/2 h	98
<i>Nitriles</i>		
cyclo-C ₆ H ₁₁ CH ₂ NH ₂	10.4.7/1 h	76
<i>n</i> -C ₈ H ₁₇ NH ₂	10.4.7/35 min	60

10.4.7 Oxidation of amines

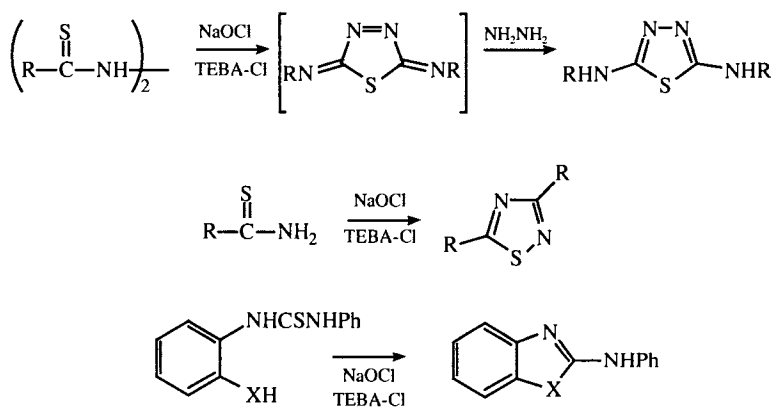
The amine (0.01 mol) and TBA-HSO₄ (0.096 g, 0.34 mmol) in EtOAc (25 ml) are stirred at room temperature with aqueous NaOCl (10%, 50 ml, 0.079 mol). On completion of the reaction, as shown by GLC, the aqueous phase is separated and extracted with EtOAc (2 × 20 ml). The combined organic solutions are dried (MgSO₄) and evaporated. The residue is taken up in aqueous NaHCO₃ (1M, 10 ml), filtered, and then stirred with aqueous HCl (10%, 25 ml) for 10 min at room temperature and 15 min at 100°C. The cooled solution is extracted with CH₂Cl₂ (20 ml) and the dried (MgSO₄) organic extract is evaporated to yield the ketone or nitrile.

Toluene has been converted into benzyl chloride (67%) by hypochlorite under phase-transfer conditions, but the procedure does not appear to have been exploited generally, possibly because of competing arene epoxidation [16]. Oxidation of 2,5-di-*t*-butylfuran yields 2,2,7,7-tetramethyloct-4-en-3,6-dione (83%) [17].

The Hoffman rearrangement of amides by quaternary ammonium hypochlorites is not particularly efficient under phase-transfer catalytic conditions and only low yields of nitrile, aldehydes, or ketones, which result from oxidation of the amines, are

isolated [14]. However, addition of sodium bromide, which results in the formation of the quaternary ammonium tribromide, not only promotes the Hoffman degradation of the amide, but also converts the resulting amine into the nitrile in overall yields of 50–70% (see Section 9.2) [18]. In contrast, thioamides produce 1,2,4-thiadiazoles under the oxidative conditions [19], whereas 1,3,4-thiadiazoles are obtained by the oxidation of hydrazinedithiocarboxanilides, followed by reduction of the initially formed cyclic product.

Carbodiimides are rapidly and conveniently obtained from thioureas (Table 10.14) [19], whereas 2-amino- and 2-hydroxyphenylthioureas are oxidatively cyclized to benzimidazoles and benzoxazoles, respectively (Scheme 10.2).



Scheme 10.2

TABLE 10.14
Oxidation of thioamides and thioureas

	% yield
<i>Thioamides</i>	<i>1,2,4-Thiadiazoles</i>
R = Ph	89
4-ClC ₆ H ₄	85
2-NO ₂ C ₆ H ₄	60 ^a
3-NO ₂ C ₆ H ₄	86
<i>Thioureas</i>	<i>Carbodiimides</i>
R = Ph	77
cyclo-C ₆ H ₁₁	88
2-MeC ₆ H ₄	82
2-EtOC ₆ H ₄	56
4-MeC ₆ H ₄	72
<i>2-Substituted phenyl thioureas</i>	
2-substituent = OH	65% 2-Anilinobenzoxazole
NH ₂	52% 2-Anilinobenzimidazole

^a + 28% 2-O₂NC₆H₄CN.

10.4.8 Hypochlorite oxidation of thioureas, thioamides and hydrazinedithiocarboxanilides

The thiocarbonyl compound (0.1 mol) is added with stirring to TEBA-Cl (0.23 g, 1 mmol) in CH_2Cl_2 (250 ml). Aqueous NaOCl (20%, 150 ml) is added dropwise. The mixture is stirred for a further 20–30 min until all of the thiocarbonyl compound has dissolved. The aqueous phase is then separated and extracted with CH_2Cl_2 (2×10 ml). The combined organic solutions are dried (MgSO_4) and evaporated to yield the appropriate product.

Sulphoximes are obtained by a facile oxidation of sulphilimines [20]. The reaction, which can be conducted in ethyl acetate and/or dichloromethane, is best catalysed by tetra-*n*-butylammonium bromide or Adogen. Benzyltriethylammonium chloride has no significant catalytic activity.

10.4.9 Oxidation of sulphilimines

Aqueous NaOCl (10%, 4.2 ml, 5.6 mmol) is added with stirring to the sulphilimine (2.8 mmol) and TBA-Br (0.4 g, 1.2 mmol) in EtOAc (20 ml) and CH_2Cl_2 (20 ml). The mixture is stirred at room temperature until all the sulphilimine has been consumed, as analysed by TLC, and the organic phase is then separated, washed with H_2O (2×10 ml), dried (MgSO_4), and evaporated to yield the sulphoxime (Table 10.15).

Aliphatic nitro compounds are converted into the corresponding carbonyl derivatives (Table 10.16) using sodium chlorite under basic conditions in the presence of a

TABLE 10.15
Oxidation of (*N*-arenesulphonyl)sulphilimines

$\text{R}^1(\text{S}=\text{NTos})\text{R}^2$		% yield of sulphoxime
$\text{R}^1 = \text{Me}$	$\text{R}^2 = \text{Me}$	12 ^a
	$-(\text{CH}_2)_4-$	77
	$-(\text{CH}_2)_5-$	74
Me	Ph	92
Me	4-MeC ₆ H ₄	82
Me	4-MeOC ₆ H ₄	80
Me	4-ClC ₆ H ₄	86
Ph	cyclo-C ₃ H ₅	80
Ph	cyclo-C ₅ H ₉	78
Ph	cyclo-C ₆ H ₁₁	73
Et	Ph	90
Ph	Ph	98 ^b
Ph	4-ClC ₆ H ₄	93
Ph	4-MeC ₆ H ₄	93
Ph	4-MeOC ₆ H ₄	90
Ph	4-O ₂ NC ₆ H ₄	94
Ph	3-MeC ₆ H ₄	90
Ph	1-naphthyl	95

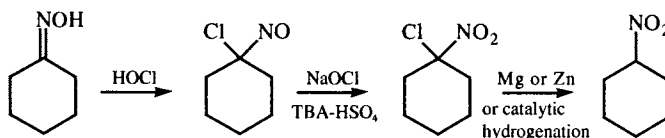
^a 83% using TBA-HSO₃, ^b 100% using Adogen.

TABLE 10.16

Selected examples of the oxidative conversion of nitro compounds into carbonyl derivatives

Nitroalkane	Product	Reaction time	% yield
cyclo-C ₆ H ₁₁ NO ₂	cyclohexanone	8 h	85
4-MeC ₆ H ₄ CH ₂ CH(NO ₂)Me	4-MeC ₆ H ₄ CH ₂ COMe	24 h	65
EtCOCH(CH ₂ NO ₂)Me	EtCOCH(CHO)Me	1 h	67
<i>n</i> -C ₆ H ₁₃ NO ₂	<i>n</i> -C ₅ H ₁₁ CHO	45 min	70
MeCH(NO ₂)(CH ₂) ₂ COMe	MeCO(CH ₂) ₂ COMe	7 h	75
EtOCO(CH ₂) ₃ NO ₂	EtOCO(CH ₂) ₄ CHO	1 h	65

quaternary ammonium salt (*cf.* the perruthenate oxidation, **10.6.22**) [21]. The reverse conversion of carbonyl compounds into nitro derivatives has also been reported [22]; the key step involves the oxidation of the intermediate chloro nitroso derivative by sodium hypochlorite under phase-transfer catalytic conditions (Scheme 10.3).



Scheme 10.3

10.4.10 Oxidation of nitro compounds

The nitro compound (5 mmol) in CH₂Cl₂ (15 ml) and TBA-HSO₄ (0.17 g, 0.5 mmol) are cooled to 0°C and aqueous NaOH (1M, 15 ml) is added, followed by solid NaClO₂ (68 mg, 0.75 mmol). After 10 min at 0°C, the mixture is stirred at room temperature (Table 10.16). The aqueous phase is separated and extracted with CH₂Cl₂ (2 × 10 ml). The combined organic solutions are washed with brine (25 ml), dried (MgSO₄), and evaporated to yield the carbonyl compound.

10.4.11 Conversion of carbonyl compounds into nitro compounds

Aqueous HOCl (0.27 M, 18.5 ml) is added to the oxime (5 mmol) in PhH (25 ml) and the mixture is stirred at room temperature for 25 min. The blue organic phase is separated and TBA-HSO₄ (0.58 g, 1.7 mmol) and aqueous NaOCl (0.5 M, 20 ml) are added. The mixture is stirred for a further 45 min at 27°C until the blue colour has faded. Reductive dehalogenation of the chloro nitro derivative can be effected by (a) addition to Mg in THF, (b) the addition of Zn dust in aqueous THF and NH₂OH, or (c) by catalytic hydrogenation over Pd/C in methanolic NaOH.

Cycloalkanones are oxidatively cleaved to yield dicarboxylic acids, together with their chlorinated derivatives [23]. The initial α-chlorination is followed by solvolysis

to yield the α -diketone, which then undergoes oxidative cleavage or further chlorination, followed by oxidative cleavage. For maximum yields, a pH of 12.0 should be maintained.

10.4.12 Oxidative cleavage of cycloalkanones

Aqueous NaOCl (10%, 400 ml) is added with stirring to the cycloalkanone (0.1 mol) and Aliquat (4 g, 10 mmol) at 10°C. The mixture is stirred and the pH is maintained at 12.0 by the addition of aqueous NaOH (0.5 M). On completion of the reaction, the aqueous phase is separated, washed with CH_2Cl_2 (200 ml), and acidified to pH 2.0 with HCl (2M). The acidic solution is cooled to 0°C to cause precipitation of the dicarboxylic acids (e.g. cyclohexanone yields a mixture of adipic acid 63%, succinic acid 9%, glutaric acid 17%, and α,α -dichloroadipic acid 5%).

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10.5. IRON(III) AND CERIU(IV) OXIDATIONS

The use of cerium(IV) salts as catalytic oxidation mediator is restricted by their insolubility in non-aqueous media. Cerium(IV) ammonium nitrate (CAN) may be used in organic solvents upon the addition of quaternary ammonium salts, but cerium(IV) sulphate is not transferred under analogous conditions. Bis(tetra-*n*-butylammonium) hexanitratocerate(IV) is obtained in a solid form by metathesis of CAN

with tetra-*n*-butylammonium hydrogen sulphate [1]. Disubstituted sulphides are oxidized to the corresponding sulfoxides in 90–100% yields by CAN in the presence of tetra-*n*-butyl-ammonium bromide [2].

10.5.1 Bis(tetra-*n*-butylammonium)hexanitratocerate(IV)

TBA-HSO₄ (3.4 g, 10 mmol) in CH₂Cl₂ (50 ml) is shaken with aqueous CAN (sat. soln, 3 × 10 ml) and the organic phase is then dried (Na₂SO₄) and evaporated to yield (TBA)₂[Ce(NO₃)₆], m.p. 150–152 °C.

10.5.2 Oxidation of sulphides

CAN (2.9 g, 5.25 mmol) in H₂O (15 ml) is added to the sulphide (2.5 mmol) and TBA-Br (0.16 g, 0.5 mmol) in CH₂Cl₂ (130 ml) at room temperature and the mixture is stirred until the reaction is complete (10–20 min for dialkyl and alkyl aryl compounds, 6 h for diaryl sulphides). The organic phase is separated, washed with H₂O (2 × 100 ml), dried (Na₂SO₄), and evaporated to yield the sulfoxide [*n*-Bu₂SO, 100%; PhSOMe, 98%; PhCH₂SOPh, 99%; (PhCH₂)₂SO, 97%; Ph₂SO, 96%].

Catalytic amounts of cerium (IV) and silver (I) have also been used as oxidation mediators for the conversion of arenes into quinones under liquid:liquid phase-transfer catalytic conditions using ammonium peroxysulphate to re-oxidize the cerium(III) to cerium(IV). A systematic study of the system indicates that the re-oxidation step occurs in the aqueous phase and that the silver ion also remains in the aqueous phase, whereas the oxidation of the arene occurs in the organic phase [1]. Higher yields and/or shorter reaction times are achieved when the predominant counter anion is nitrate (10.5.3.C) [3]. The procedure has been applied to the conversion of arenes into quinones, and methylarenes into the corresponding aldehydes, although the yields vary depending on other substituents on the aromatic ring and the products are frequently contaminated by traces of the benzyl alcohols, benzoic acids and benzyl nitrates [3].

10.5.3 Oxidation of arenes to quinones (Table 10.17)

Method A: The arene (4 mmol) in petroleum ether (b.p. 60–80 °C, 15 ml) is added to CAN (1.1 g, 2 mmol), AgNO₃ (0.1 g, 0.6 mmol), (NH₄)₂S₂O₈ (3.5 g, 15 mmol), and TBA-HSO₄ (0.14 g, 0.4 mmol) in H₂SO₄ (0.4 M, 35 ml) and the mixture is stirred at 50 °C. The reaction mixture is cooled and the aqueous phase is separated and extracted with Et₂O (3 × 20 ml). The combined organic solutions are washed with H₂O (3 × 20 ml), dried (Na₂SO₄), and evaporated to yield the quinone.

Method B: CAN (2.1 g, 4 mmol) and TBA-HSO₄ (0.136 g, 0.4 mmol) are added to the arene (2 mmol) in CHCl₃ (20 ml) and the mixture is refluxed for *ca.* 15 h. The reaction mixture is filtered and evaporated to yield the quinone.

Method C: The arene (2 mmol), CAN (8.25 g, 15 mmol), TBA-NO₃ (1.0 g, 3.5 mmol), HNO₃ (3.5M, 50 ml) and Cl(CH₂)₂Cl (60 ml) are stirred at 45 °C until the arene has been consumed (monitor by GLC after first washing the samples with FeSO₄). The organic

TABLE 10.17
Oxidation of arenes to quinones

Arene	Reaction conditions	% yield
Naphthalene	10.5.3.A /4 h	60 ^{a,b}
	10.5.3.C /40 min	78
Anthracene	10.5.3.A /7 h	50 ^b
	10.5.3.B /15 h	95
	10.5.3.C / <5 min	55
Phenanthrene	10.5.3.A /7 h	59

^a 70% can be obtained after 1.5 h, when $n\text{-C}_{12}\text{H}_{25}\text{OSO}_2\text{Na}$ (0.8 mmol) is added. ^b 26–29% in absence of TBA- HSO_4 .

phase is separated and washed with FeSO_4 (5 ml). The aqueous phase is extracted with Et_2O (3×15 ml) and the combined organic solutions are dried (MgSO_4) and evaporated to yield the quinone.

10.5.4 Oxidation of methylarenes

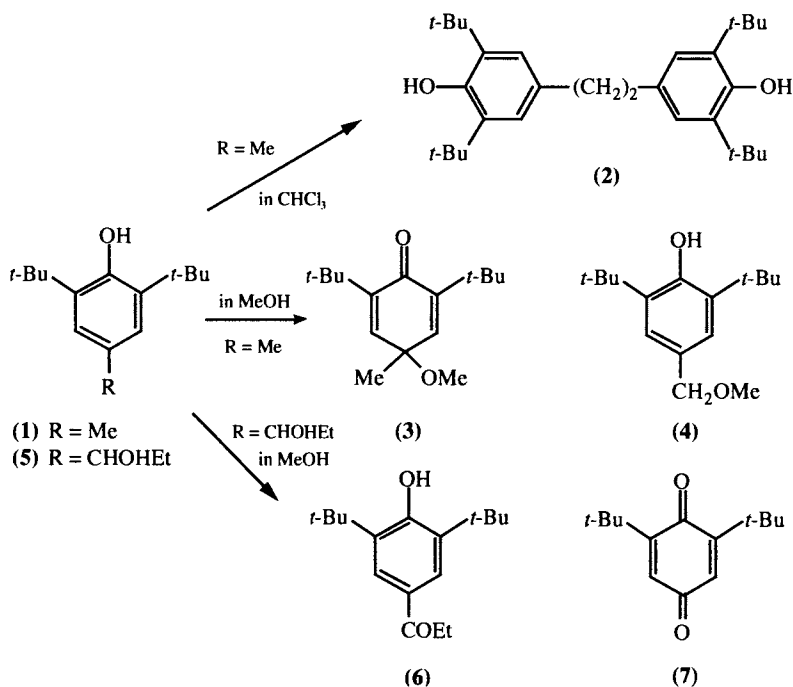
The methylarene (5 mmol), CAN (11 g, 20 mmol), HNO_3 (3.5M, 50 ml) and TBA- NO_3 (0.75 g, 2.5 mmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (30 ml) are heated at 72°C . The reaction products are isolated as described in **10.5.3.C** [e.g. 76% 4- $\text{MeC}_6\text{H}_4\text{CHO}$ from 1,4- $\text{Me}_2\text{C}_6\text{H}_4$ (35 min); 28% 4- $\text{MeOC}_6\text{H}_4\text{CHO}$ from 4- $\text{MeOC}_6\text{H}_4\text{Me}$ (<2 min at 45°C); 41% PhCHO from PhMe (1 h)].

Ferrate salts have been used under phase-transfer catalytic conditions for the oxidation of alcohols. Selective oxidation of allylic and benzylic alcohols to the corresponding aldehydes occurs under mild conditions [4].

10.5.5 Selective oxidation of allylic and benzylic alcohols

Aqueous NaOH (10%, 10 ml) is added to the alcohol (2.5 mmol), TEBA- Cl (68 mg, 0.25 mmol) and K_2FeO_4 (1.98 g, 10 mmol) in PhH (10 ml) and the mixture is stirred at room temperature until the alcohol is fully consumed, as shown by TLC analysis. The aqueous phase is extracted with PhH (10 ml) and the combined organic solutions are washed with H_2O (5 ml), dried (MgSO_4), and fractionally distilled to give the aldehyde [e.g. PhCHO (5 min), 96%; PhCOPh (6 h), 90%; PhCOMe (2 h), 91%; PhCH=CHCHO (1.5 h) 95%; PhCH=CHCOMe (8 h), 81%; PhCH=CHCOPh (9 h), 80%; MeCH=CHCHO (using 0.99 g of K_2FeO_4 at 0°C with 1% aq. NaOH), 76%].

Complex iron(III) salts are frequently used in oxidative arene coupling reactions and quinone formation and tetra- n -butylammonium hexacyanoferrate(III) has several advantages in its use over more conventional oxidative procedures. When used as the dihydrogen salt, $\text{Bu}_4\text{N}[\text{H}_2\text{Fe}(\text{CN})_6]$, it oxidizes 2,6-di- t -butyl-4-methylphenol (**1**) to the coupled diarylethane (**2**), or aryl ethers (**3**) and (**4**) (Scheme 10.4), depending on the solvent. It is noteworthy that no oxidation occurs even after two days with the tris-ammonium salt.



Scheme 10.4

Under traditional conditions with the hexacyanoferrate ion, the major product from (1) is the quinonoid ether (3), whereas it is the minor product under phase-transfer catalytic conditions. Similarly, the carbinol (5) is oxidized to the ketone (6) by the quaternary ammonium salt, whereas the quinone (7) is obtained in the absence of the quaternary ammonium ion [5].

10.5.6 Tris(tetra-*n*-butylammonium)hexacyanoferrate(III)

A saturated aqueous solution of $\text{K}_3[\text{Fe}(\text{CN})_6]$ is made alkaline by the addition of TBA-OH. The aqueous solution is extracted with CHCl_3 and the combined extracts are washed with H_2O and dried (CaSO_4). Evaporation of the solvent gives the green $(\text{TBA})_3-[\text{Fe}(\text{CN})_6]$.

10.5.7 Oxidation of 2,6-di-*t*-butylphenols with $\text{Bu}_4\text{N}[\text{H}_2\text{Fe}(\text{CN})_6]$

Method A: $(\text{TBA})_3-\text{Fe}(\text{CN})_6$ (1.97 g, 2.1 mmol) and 4-TosOH (0.76 g, 4.2 mmol) are added to the phenol **1** (0.2 mmol) in CHCl_3 (10 ml) and the mixture is allowed to stand at room temperature for 12 h. Et_2O (30 ml) and H_2O (20 ml) are added and the organic phase is separated, washed with H_2O (2×25 ml), dried (MgSO_4), and evaporated to give **2**.

Method B: $(\text{TBA})_3-\text{Fe}(\text{CN})_6$ (1.97 g, 2.1 mmol) and 4-TosOH (0.76 g, 4.2 mmol) are added to the phenol **1** or **5** in MeOH (10 ml) and the mixture is allowed to stand for 1 h. H_2O (25 ml) is added and the aqueous solution is extracted with Et_2O (2×25 ml). Evaporation of the dried (MgSO_4) ethereal extracts yields **3** and **4** (from **1**) and **6** (from **5**).

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10.6 PEROXY ACID OXIDATIONS

Adogen has been shown to be an excellent phase-transfer catalyst for the percarbonate oxidation of alcohols to the corresponding carbonyl compounds [1]. Generally, unsaturated alcohols are oxidized more readily than the saturated alcohols. The reaction is more effective when a catalytic amount of potassium dichromate is also added to the reaction mixture [1]; comparable results have been obtained by the addition of catalytic amounts of pyridinium dichromate [2]. The course of the corresponding oxidation of α -substituted benzylic alcohols is controlled by the nature of the α -substituent and the organic solvent. In addition to the expected ketones, cleavage of the α -substituent can occur with the formation of benzaldehyde, benzoic acid and benzoate esters. The cleavage products predominate when acetonitrile is used as the solvent [3].

Chromium-mediated oxidation of benzylic methylene groups to the corresponding oxo derivatives has also been reported [4]. Tri-*n*-butylstannyl chromate appears to be the best co-oxidant and a trace of 4-toluenesulphonic acid also aids the oxidation.

10.6.1 Chromate-mediated percarbonate oxidation of primary and secondary alcohols and of benzylic methylene groups

Oxidation of alcohols: $K_2Cr_2O_7$ (29 mg, 0.1 mmol) and Adogen (89 mg, 0.2 mmol) are stirred in $Cl(CH_2)_2Cl$ (10 ml) for 10 min at room temperature. The alcohol (1 mmol) and $Na_2CO_3 \cdot 1.5H_2O_2$ (0.628 g, 4 mmol) are added and the mixture stirred under reflux for 24 h. The mixture is cooled to room temperature, filtered, and the filtrate is washed well with aqueous Na_2CO_3 (sat. soln., 4×25 ml), dried (Na_2SO_4), and evaporated to yield the carbonyl compound (Table 10.18).

Oxidation of methylene groups: The alcohol (1 mmol) and $Na_2CO_3 \cdot 1.5H_2O_2$ (1.26 g, 8 mmol) and 4-TosOH (17 mg, 0.1 mmol) are added to $(n-Bu_3SnO)_2CrO_2$ (70 mg, 0.1 mmol) and Adogen (89 mg, 0.2 mmol) in MeCN (10 ml). The mixture is refluxed for ca. 20 h. and the cooled reaction mixture is then filtered and the filtrate evaporated. The carbonyl compound is isolated by flash chromatography of the residue from silica (Table 10.19).

The oxidation of alcohols by sodium percarbonate is also promoted by the addition of molybdenyl acetoacetate [5] and yields are comparable with those obtained by the chromate mediated reactions.

TABLE 10.18
Chromate-aided percarbonate oxidation of alcohols

Alcohol	% yield ^a of carbonyl compound	Alcohol	% yield ^a of carbonyl compound
<i>n</i> -C ₁₆ H ₃₃ OH	15 (23)	Nerol	74 (80)
3-Me-cyclo-C ₆ H ₁₀ OH	21 (16)	Isophorol	64 (74)
PhCH ₂ OH	85 (90)	Indan-1-ol	77 (86)
PhCH(OH)CH ₂ Me	64 (61)	Tetral-1-ol	80 (80)
PhCH=CHCH ₂ OH	87 (82)	Fluoren-9-ol	91 (91)

^a Using K₂Cr₂O₇; yields in parentheses relate to catalysis with pyridinium dichromate.

TABLE 10.19
Chromate-aided percarbonate oxidation of benzylic methylene groups

Hydrocarbon	% yield of oxidation products
PhEt	PhCOMe (32%); PhCH(OH)Me (15%); PhCO ₂ H (20%)
PhCH ₂ Ph	PhCOPh (51%); PhCH(OH)Ph (3%)
Indane	Indan-1-one (60%); indan-1-ol (10%); indan-1,3-dione (2%)
Tetralin	Tetral-1-one (68%); tetral-1-ol (7%)
Fluorene	Fluoren-9-one (63%); fluoren-9-ol (11%)

10.6.2 Molybdenum-catalysed oxidation of alcohols by sodium percarbonate (Table 10.20)

MoO₃(acac)₂ (30 mg, 0.1 mmol) and Adogen (89 mg, 0.2 mmol) are added to the alcohol (1 mmol) and Na₂CO₃·1.5H₂O₂ (0.628 g, 4 mmol) in MeCN (10 ml). The mixture is stirred under reflux and then cooled to room temperature and filtered. The filtrate is evaporated and the carbonyl compound is isolated by flash chromatography from silica.

TABLE 10.20
Selected examples of the molybdenum-catalysed oxidation of alcohols by sodium percarbonate

Alcohol	Reaction conditions	% yield of carbonyl compound
<i>n</i> -C ₁₆ H ₃₃ OH	10.6.2/24 h	53 ^a
cyclo-C ₆ H ₁₁ OH	10.6.2/18 h	94
PhCH ₂ OH	10.6.2/20 h	72
PhCH ₂ CH(OH)Me	10.6.2/24 h	95
2-NaphthylCH ₂ OH	10.6.2/22 h	67
PhCH=CHCH ₂ OH	10.6.2/9 h	63 ^b
PhCOCH(OH)Ph	10.6.2/20 h	45 ^c
Indan-1-ol	10.6.2/24 h	89 ^d
Tetral-1-ol	10.6.2/24 h	92

^a + 10% acid. ^b + 24% 1-phenyl-1,2-epoxypropan-3-ol and 9% PhCH=CHCO₂H. ^c + 35% PhCO₂H. ^d 97% in Cl(CH₂)₂Cl.

Although there are other convenient procedures for the conversion of sulphides into sulfoxides and sulphones, the phase-transfer catalysed reaction using Oxone[®] has the advantage that the oxidation can be conducted in the presence of other readily oxidized groups, such as amines, alkenes, and hydroxyl groups, and acid-labile groups, such as esters and carbamates [6, 7]. Hydrolysis of very acid-labile groups, such as ketals, can result in production of the keto sulphone.

Cation exchange produces 'tetra-*n*-butylammonium hydrogen persulphate' [6, 7] which, as with other peroxy compounds, should be treated as POTENTIALLY EXPLOSIVE.

With the preformed ammonium persulphate, oxidation of sulphides to both sulfoxides and sulphones has been observed [e.g. 6, 7] whereas, when Oxone[®] is used in conjunction with a quaternary ammonium salt, oxidation can be selectively stopped at the sulfoxide stage [6–8]. It has been recorded that electron-deficient aryl sulphides, e.g. di(4-nitrophenyl)sulphide, are not readily oxidized.

10.6.3 'Tetra-*n*-butylammonium hydrogen persulphate'

Oxone[®] (10.86 g, 17.7 mmol) in H₂O (45 ml) is stirred with TBA-HSO₄ (30 g, 88 mmol) for 30 min at room temperature. The aqueous solution is extracted with CH₂Cl₂ (3 × 70 ml), and the dried (MgSO₄) organic extracts are evaporated to give the ammonium salt (89%).

10.6.4 Oxidation of sulphides to sulphones with Oxone[®] (Table 10.21)

Method A: TBA-Oxone (0.98 g, 0.6 mmol) is added to the sulphide (0.2 mmol) in CH₂Cl₂ (10 ml). The mixture is stirred at room temperature until all of the sulphide has been consumed, as shown by TLC analysis. The sulphone is isolated by direct flash chromatography of the reaction mixture on silica.

Method B for potentially acid-labile compounds: TBA-Oxone (0.98 g, 0.6 mmol) and anhydrous Na₂CO₃ (0.64 g, 0.6 mmol) suspended in CH₂Cl₂ (10 ml) are added to the sulphide (0.2 mmol) and the mixture is stirred at room temperature until all of the sulphide has been consumed. The mixture is diluted with Et₂O (15 ml). The organic phase is separated, washed with aqueous NaOH (2M, 25 ml), H₂O (25 ml), and brine (25 ml), dried (MgSO₄), and evaporated to yield the sulphone.

10.6.5 Oxidation of sulphides to sulfoxides with Oxone[®] (Table 10.22)

Method A: Aqueous Oxone[®] (1.75 g in 10 ml H₂O) is added with stirring at –10°C to the sulphide (1.42 mmol) and TBA-Br (23 mg, 0.07 mmol) in CH₂Cl₂ (75 ml). The mixture is allowed to come to room temperature and is stirred for a further 18 h. Aqueous NaHSO₃ (10%) is added and the organic phase is separated, dried (MgSO₄), and evaporated to yield the sulfoxide.

Method B: (TBA)₂-S₂O₈ (0.68 g, 1.0 mmol) in CH₂Cl₂ (5 ml) is stirred at room temperature with the sulphide (1.0 mmol) in CH₂Cl₂ (3.5 ml) for 1.5 h. The organic solution is poured into H₂O (25 ml) and the mixture is extracted with CH₂Cl₂ (4 × 15 ml). The combined organic extracts are washed with H₂O (3 × 25 ml), dried (Na₂SO₄), and evaporated to yield the sulfoxide.

TABLE 10.21
Selected examples of the oxidation of sulphides to sulphones using Oxone®

R ¹ SR ²		Reaction conditions	% yield
R ¹ = Ph	R ² = Me	10.6.4.A/96 h	78
Ph	cyclohex-2-enyl	10.6.4.A/46 h	79
Ph	CH ₂ COMe	10.6.4.A/25 h	83
Ph	(CH ₂) ₃ CH=CH ₂	10.6.4.A/22 h	81
Ph	CH ₂ CH=CHPh	10.6.4.A/22 h	76
Ph	(CH ₂) ₃ CH=CHTMS	10.6.4.A/48 h	81
		10.6.4.B/24 h	78
Ph	Geranylgeranyl	10.6.4.A/24 h	49
		10.6.4.B/96 h	54
Ph	(CH ₂) ₃ THP	10.6.4.A/36 h	71
		10.6.4.B/48 h	85
Ph	(CH ₂) ₃ C(OMe) ₂ Me	10.6.4.B/22 h	72
Ph	(CH ₂) ₄ CH(OMe) ₂	10.6.4.B/30 h	84
Ph	2-PyridylCH ₂	10.6.4.A/24 h	76
Me	CH ₂ CH(NH ₃ Cl)CO ₂ Me	10.6.4.A/22 h	33
MeCH(OH)CH ₂	CH ₂ CH(NHBoc)CO ₂ Bz	10.6.4.A/64 h	58

TABLE 10.22
Selected examples of the oxidation of sulphides to sulfoxides

R ¹ SR ²		Method	% yield of sulfoxide	% yield of sulphone
R ¹ = Ph	R ² = Ph	10.6.5.A	30	70
		10.6.5.B	99	0
4-MeC ₆ H ₄	4-MeC ₆ H ₄	10.6.5.A	66	34
4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	10.6.5.A	93	7
4-CNC ₆ H ₄	4-CNC ₆ H ₄	10.6.5.A	83	17
2-CNC ₆ H ₄	2-CNC ₆ H ₄	10.6.5.A	5	0 ^a
Et	Et	10.6.5.B	98	0
PhCH ₂	PhCH ₂	10.6.5.A	70	30
		10.6.5.B	98	0
Me	Ph	10.6.5.A	99	0

^a 95% recovered sulphide; 69% sulfoxide after 13 days.

Primary and secondary alcohols are oxidized to the corresponding carbonyl compounds by tetra-*n*-butylammonium persulphate in dichloromethane but, when the reaction is conducted in tetrahydropyran, tetrahydropyranyl ethers (>90%) are formed by a direct one-electron oxidative reaction of tetrahydropyran with the alcohol [9]. Tetrahydrofuranyl ethers have been prepared by an analogous method [10, 11].

10.6.6 Tetrahydropyranyl and tetrahydrofuranyl ethers

The alcohol (1 mmol) and $(\text{TBA})_2\text{-S}_2\text{O}_8$ (0.98 g, 1.4 mmol) in THF or THP (10 ml) are stirred under reflux for 3 h. The solvent is evaporated under reduced pressure and H_2O (25 ml) is added to the residue, which is then extracted with Et_2O (2×15 ml). The extracts are dried (MgSO_4) and evaporated to yield the tetrahydrofuranyl or tetrahydropyranyl ether.

Aromatic amines are oxidized by Oxone[®] in acetone to produce the corresponding nitro arenes in good to high yield (50–100%) [12]. The reaction is thought to proceed via the initial formation of dimethyldioxirane. Electron excessive heteroarenes, which are normally very susceptible to oxidation are untouched by the reaction.

10.6.7 Oxidation of aminoarenes

Oxone[®] (20 g, 32 mmol) in H_2O (150 ml) is added with stirring to the aminoarene (10 mmol) in CH_2Cl_2 (100 ml), Me_2CO (100 ml), aqueous Na_3PO_4 (0.8 M, 50 ml) and TBA-HSO_4 (0.17 g, 0.5 mmol) with the concomitant addition of aqueous KOH (2M) to maintain the pH between 7.5 and 8.5. The mixture is stirred at 0°C for 15 min and Me_2S (1 ml) is then added. The organic phase is separated from the filtered mixture, washed with H_2O (50 ml), dried (MgSO_4), and evaporated to give the nitroarene, ArNO_2 (e.g. Ar = Ph, 78%; 2-MeOC₆H₄, 100%; 3-MeOC₆H₄, 73%; 5-nitroindole, 58% with 5-nitroso compound).

As an alternative to simple solvolysis, tosylhydrazones have been oxidatively cleaved to the corresponding ketones in high yield (>90%) using tetra-*n*-butylammonium persulphate [13]. The reaction has been applied with success even with unsaturated ketones.

Epoxidation of alkenes can be effected by potassium persulphate. When the oxidation is conducted in the presence of chiral trifluoroketones, chiral oxiranes (ee 12–22%) are produced [14]. The chirality appears to be achieved via the initial reaction of the persulphate with the ketone to generate chiral dioxiranes, which then interact with the alkenes.

10.6.8 Chiral oxiranes

The alkene (5 mmol) and the chiral trifluoroketone, e.g. (+)-3-trifluoroacetylcamphor (4–6 mmol) in CH_2Cl_2 (50 ml) are added to aqueous phosphate buffer (pH 7.5, 50 ml), TBA-HSO_4 (15 mg, 0.04 mmol) and EDTA-Na_2 (15 mg). The mixture is stirred at room temperature and aqueous KHSO_5 (0.6 M, 20 ml) is added slowly over 30–60 min while the pH 7.5 is maintained by the addition of aqueous KOH (1 M). Oxone[®] (15 g) is added over 24 h at room temperature and pH 7.5. The reaction is monitored by GLC and more Oxone[®] is added, if necessary. When complete, the reaction mixture is filtered and the aqueous phase is separated and extracted with CH_2Cl_2 (2×25 ml) and Et_2O (2×20 ml). The combined organic solutions are dried (MgSO_4) and evaporated to yield the oxirane [e.g. 82% 1*R*,2*R*-oxirane from *trans*-PhCH=CHMe (ee 13%)].

Water-insoluble carboxylic acids are oxidized in high yield to corresponding peracids by potassium persulphate in the presence of a phase-transfer catalyst. The overall yields are *ca.* 25–30% higher than those obtained in the absence of the catalyst. [15].

10.6.9 Peracid formation

$K_2S_2O_8$ (0.54 g, 2 mmol) in H_2O (15 ml) is added to the carboxylic acid (1 mmol) and TEBA-Cl (0.02 g, 0.1 mmol) in Et_2O or CH_2Cl_2 (15 ml) and the mixture is stirred at 20 °C for *ca.* 15 h. The organic phase is separated, washed well with H_2O and dried ($MgSO_4$) to give an organic solution of the peracid, the concentration of which can be determined by titration with K_2CS_3 .

The phase-transfer catalysed oxidative iodination of α,β -unsaturated carbonyl compounds (Table 10.23) using iodine/persulphate to produce the α -iodo derivatives has been described [16]. Activated methylene groups are also iodinated under similar conditions.

TABLE 10.23

Selected examples of α -iodination of α,β -unsaturated carbonyl compounds and activated methylene groups

Carbonyl compound	Product	% yield
cyclohex-2-enone	2-Iodocyclohex-2-enone	85
cyclopent-2-enone	2-Iodocyclopent-2-enone	83
Uracil	5-Iodouracil	72
1,3-Dimethyluracil	5-Iodo-1,3-dimethyluracil	75
$PhCH=CHCOMe$	$PhCH=CHCOCH_2I$	95
$MeCOCH_2CO_2Et$	$MeCOCHICO_2Et$	90

10.6.10 α -Iodination reactions

The carbonyl compound (1.0 mmol) in dry MeCN is added to $(TBA)_2S_2O_8$ (0.43 g, 1 mmol) and iodine (0.25 g, 1 mmol) in MeCN (5 ml) and the mixture is stirred at room temperature until the reaction is shown to be complete by TLC analysis. The mixture is then poured into aqueous $NaHSO_3$ (10%, 30 ml) and extracted with EtOAc (3×30 ml). The combined organic solutions are washed with H_2O (3×40 ml), dried ($MgSO_4$), and evaporated to yield the iodo derivative.

Sodium perborate oxidation of alcohols by is aided by Aliquat, but also requires the addition of chromium oxide [17]. However, the long reaction times at 60–80 °C and the variable yields do not make the procedure particularly attractive. In contrast, direct epoxidation of α,β -unsaturated ketones has been conducted with moderate success using sodium perborate catalysed by tetra-*n*-hexylammonium hydrogen sulphate [18, 19].

10.6.11 Epoxidation of α,β -unsaturated ketones (Table 10.24)

The α,β -unsaturated ketone (10 mmol) in CH_2Cl_2 (10 ml) is stirred at 27°C with aqueous NaBO_3 (sat. soln. 90 ml) containing NaOH (10 mmol) and $\text{THA}\cdot\text{HSO}_4$ (23 mg, 0.5 mmol). The oxirane is isolated using a procedure analogous to that described in 10.4.4.

TABLE 10.24
Epoxidation of α,β -unsaturated ketones using sodium perborate

Alkene	Reaction conditions	% yield of epoxy ketone ^a
$\text{Me}_2\text{C}=\text{CHCOMe}$	10.6.11/2 h	95 ^b
Isophorone	10.6.11/72 h	93 ^c
$\text{PhCH}=\text{CHCOPh}$	10.6.11/10 min	80
$\text{PhCH}=\text{CHCHO}$	10.6.11/3 h	trace ^d
Naphthaquinone	10.6.11/10 min	24 ^e

^a By GLC analysis. ^b 73% in absence of solvent after 15 min. ^c 95% in absence of solvent after 1 h.

^d 75% PhCHO isolated. ^e No NaOH added.

The addition of benzyltriethylammonium chloride promotes the perborate-mediated Baeyer–Villiger oxidation of water-immiscible ketones [20].

Quaternary ammonium periodates, prepared either from periodic acid and the quaternary ammonium hydroxide [21, 22] or by metathesis from sodium periodate and a quaternary ammonium salt [e.g. 23–25], have been used for a range of oxidations at stoichiometric levels in two-phase systems [21–33]. The tetra-*n*-butylammonium and hexadecyltrimethylammonium salts are both highly soluble in organic solvents (considerably less so in water), whereas benzyltriethylammonium periodate has a lower solubility and stability than either salt.

10.6.12 Tetra-*n*-butylammonium periodate

NaIO_4 (21.4 g, 0.1 mol) in H_2O (150 ml) is stirred with $\text{TBA}\cdot\text{HSO}_4$ (34 g, 0.1 mol) in H_2O (50 ml). $\text{TBA}\cdot\text{IO}_4$ (ca. 100%) m.p. $158\text{--}159^\circ\text{C}$ precipitates from solution.

One of the earliest examples of its application describes the oxidation with tetraethylammonium periodate of oximes to nitroso compounds [21, 22] and the same reagent has subsequently be used in the preparation of the transient nitroso compounds by oxidation of *N*-hydroxyureas [21, 22] and benzhydroxamic acids [26].

Although there are other more cost effective and efficient procedures, the periodate oxidation of dialkyl sulphides to the sulfoxides has been shown to proceed in high yield [24, 25, 29]; thiols are oxidized to disulphides (95–100%) [29]. The potency of the quaternary ammonium periodate for the oxidation of sulphides is improved by the addition of *meso*-tetraphenylporphinatoiron(III) chloride [TPPFe(III)Cl] [27]. In contrast with the oxidation conducted in the absence of TPPFe(III)Cl [24, 25], aryl sulphides are oxidized more rapidly than alkyl sulphides.

An oxometalloporphyrin is probably the actual oxidizing agent; the threo:erythro ratio (35:65) of the diastereomeric sulfoxides obtained from racemic sulphides is close to that obtained for the corresponding oxidation using cytochrome P450 oxidase and differs from that (58:42) obtained by the oxidation using periodate in the absence of the porphyrin [27]. The cytochrome-induced demethylation of *N,N*-dimethylaniline can also be mimicked with periodate and the metalloporphyrin.

10.6.13 Oxidation of unprotected carbohydrate hydroxyl groups

The carbohydrate (20 mmol) in EtOH-free CHCl_3 (25 ml) is stirred with TEBA-Cl (0.23 g, 1 mmol), NaIO_4 (5.3 g, 25 mmol), RuO_2 (50 mg) and K_2CO_3 (0.75 g) in H_2O (25 ml) for 48 h at room temperature. When the reaction is complete, as shown by TLC analysis, Me_2CHOH (5 ml) is added and the mixture is filtered thorough Celite. The organic phase is separated from the filtrate, dried (MgSO_4), and evaporated to yield the oxidized carbohydrate (>70%).

10.6.14 Periodate oxidation of sulphides, R^1SR^2 (Table 10.25)

Method A: The sulphide (0.03 mol) is added to TBA- IO_4 (13.0 g, 30 mmol) in CHCl_3 (50 ml) and the mixture is refluxed until the sulphide has been consumed, as shown by GLC. The cooled mixture is filtered through silica and evaporated to yield the sulfoxide.

Method B: The sulphide (1 mmol), TBA- IO_4 (0.47 g, 1.1 mmol) and TPPFe(III)Cl (0.01–0.03 mmol) in CHCl_3 (5 ml) are stirred at room temperature for 1.5 h. The reaction is monitored by TLC and, when complete, the reaction mixture is directly chromatographed on silica to yield the sulfoxide

TABLE 10.25
Oxidation of sulphides to sulfoxides

R^1SR^2	TPPFe(III)Cl	Reaction conditions	% yield
$\text{R}^1 = t\text{-Bu}$ $\text{R}^2 = t\text{-Bu}$	13 mmol	10.6.14/20 h	90 ^a
PhCH ₂ <i>sec</i> -Bu	9 mmol	10.6.14/11 h	87
PhCH ₂ PhCH ₂	15 mmol	10.6.14/7 h	80
-(CH ₂) ₄ -	—	10.6.14/2 h	90
-(CH ₂) ₂ CH(4-ClC ₆ H ₄)(CH ₂) ₂ -	10 mmol	10.6.14/10 h	90
4-MeC ₆ H ₄ Me	—	10.6.14/4 h	86
4-MeC ₆ H ₄ <i>n</i> -Bu	—	10.6.14/4 h	85
-(<i>o</i> -C ₆ H ₄)CH ₂ CHMe-	10 mmol	10.6.14/8 h	83
Ph Ph	—	10.6.14/8 h	72
	30 mmol	10.6.14/2 h	95
-(<i>o</i> -C ₆ H ₄)-(<i>o</i> -C ₆ H ₄)-	20 mmol	10.6.14/1.5 h	84
-(<i>o</i> -C ₆ H ₄)-O-(<i>o</i> -C ₆ H ₄)-	17 mmol	10.6.14/2 h	96
4-O ₂ NC ₆ H ₄ Ph	20 mmol	10.6.14/2.5 h	85
4-MeC ₆ H ₄ 4-MeC ₆ H ₄	—	10.6.14/7 h	70
MeCH=CHCH ₂ Me	24 mmol	10.6.14/2 h	79

^a *t*-BuSO.S.*t*-Bu isolated.

Activated methylene groups are readily oxidized to carbonyl groups, e.g. $\text{ArCHRCO}_2\text{H}$ produces ArCOR [28]. Similarly, the oxidation of α -hydroxyacids to aldehydes [24, 25] and α -hydroxyketones to α -diketones [29] using stoichiometric amounts of tetra-*n*-butylammonium periodate is almost quantitative after a relatively short reaction period. The oxidation of simple alcohols to the corresponding aldehydes is aided by the addition of boron trifluoride etherate [29]. The oxidative cleavage of the bromomethyl group of bromoacetophenones produces the corresponding benzoic acids [24, 25].

Alkenes have been oxidized to 1,2-diols (>90%) by catalytic amounts of the ammonium periodate in the presence of osmium, and stoichiometric amounts of the periodate cleave the diols to produce the dicarbonyl derivatives (>80%) [23, 30]. The procedure appears, however, to be less effective than with the quaternary ammonium permanganate.

Polymer-bound periodate and iodate have been used for the oxidation of quinols to quinones in high yield (>90%) [31].

10.6.15 Periodate oxidation of activated methylene groups ($\text{ArCHRCO}_2\text{H} \rightarrow \text{ArCOR}$)

The methylene compound (0.01 mmol) and TBA- IO_4 (43 mg, 0.01 mmol) in dioxan or CH_2Cl_2 (10 ml) are refluxed until the substrate is consumed (the solution becomes dark with the liberation of iodine). The mixture is evaporated and the residue is extracted with Et_2O (50 ml), which is then evaporated to yield the carbonyl compound [e.g. 50% PhCHO (12 h); 65% 4- $\text{ClC}_6\text{H}_4\text{CHO}$ (12 h); 70% 4- $\text{MeOC}_6\text{H}_4\text{CHO}$ (16 h); 60% 1-naphthyl CHO (8 h); 50% 2-naphthyl CHO (16 h); 85% Ph_2CO (48 h)].

10.6.16 Periodate oxidative cleavage of α -hydroxy carboxylic acids, $\text{RCHOHCO}_2\text{H}$

The α -hydroxy acid (10 mmol) is added to TBA- IO_4 (4.3 g, 10 mmol) in CHCl_3 (10 ml) and the mixture is refluxed until the acid is consumed, as shown by GLC. The purple solution is washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10%, 50 ml) and the dried (Na_2SO_4) organic phase is fractionally distilled to yield the aldehyde, RCHO [e.g. $\text{R} = \text{Ph}$, 86% (5 h); *n*-Bu, 90% (3 h); *n*-Pr, 85% (4 h); *n*- $\text{C}_{14}\text{H}_{29}$, 90% (3 h)].

10.6.17 Periodate oxidative cleavage of bromoacetophenones, ArCOCH_2Br

The bromoacetophenone (10 mmol) and TBA- IO_4 (4.3 g, 10 mmol) in dioxan (15 ml) is refluxed until the ketone is consumed. Aqueous NaHCO_3 (sat. soln 50 ml) is added and the mixture is washed well with EtOAc (3×15 ml). The aqueous phase is acidified and extracted with Et_2O (320 ml) and ethereal extract is evaporated to yield the benzoic acid [e.g. 78% PhCO_2H (15 h); 75% 4- $\text{BrC}_6\text{H}_4\text{CO}_2\text{H}$ (25 h)].

In conjunction with a ruthenium oxide co-catalyst, sodium periodate has been used as a mild oxidizing agent in the presence of benzyltriethylammonium chloride

for the oxidation of carbohydrates [32, 33]. *sec*-Hydroxyl groups of partially protected furanose and pyranose sugars are oxidized to ketones in high yield (>80%).

10.6.18 Ruthenium-promoted oxidation of carbohydrates with sodium periodate

The partially protected furanose or pyranose sugar (20 mmol) in CHCl_3 (25 ml) is stirred with NaIO_4 (5.3 g, 25 mmol), RuO_2 (50 mg, 0.4 mmol), TEBA-Cl (0.23 g, 1 mmol) and K_2CO_3 (0.75 g) in H_2O (25 ml) until TLC analysis shows complete oxidation (2–48 h). The reaction is quenched by the addition of Me_2CHOH (5 ml) and filtered through Celite. The organic phase is separated, dried (MgSO_4), and evaporated and the oxidized sugar is purified by chromatography on silica.

Although ruthenium oxide is an extremely powerful oxidizing agent, more so than osmium tetroxide, its reactivity can be controlled as the ruthenium(VI)oxo derivative or, more conveniently for use in non-aqueous media, as ruthenium(VII) as a quaternary ammonium perruthenate, Q^+RuO_4^- . Tetra-*n*-propylammonium perruthenate is an exceptionally useful mild and convenient oxidant for alcohols. In conjunction with a co-oxidant, such as *N*-methylmorpholine-*N*-oxide, it can be used at catalytic levels for the selective oxidation of alcohols to aldehydes and ketones [for comprehensive review of its properties and uses, see 34–36]. Similar oxidations of allylic and benzylic alcohols have been described using potassium persulphate as the co-oxidant [37]. Potentially labile multifunctional groups and ring systems are unaffected during the oxidation of the hydroxyl groups and the procedure has wide application, e.g. a range of hydroxy steroids have been converted into the corresponding carbonyl compounds in good yield [38]. In the majority of reactions, the addition of finely ground molecular sieves has been found to improve the rate and efficiency of the reactions. *Care should be used when handling the ammonium perruthenate. It is thermally unstable and ignites at 150–160°C. The oxidation reactions can be quite vigorous and external cooling is advisable when they are conducted on a large scale.*

10.6.19 Preparation of tetra-*n*-propylammonium perruthenate

Hydrated RuCl_3 (1.5 g, ca. 6.2 mmol) is stirred with sodium periodate (5.5 g, 26 mmol) in H_2O (50 ml) for 12 h. The precipitated ruthenium oxide is added at 0–5°C under an atmosphere of oxygen to aqueous TPA-OH (1M, 5 ml) and aqueous NaOH (0.8 M, 50 ml). Precipitated TPA- RuO_4 (87%) is collected and washed well with H_2O and dried under vacuum.

10.6.20 General procedure for oxidation of alcohols with TPA- RuO_4 (Table 10.26)

Method A: The alcohol (0.5 mmol) and *N*-methylmorpholine-*N*-oxide (0.1 g, 0.75 mmol) are stirred in CH_2Cl_2 (10 ml) with 4Å molecular sieves for 10 min. TPA- RuO_4 (0.025 mmol) is then added and the reaction is monitored by TLC analysis. Upon comple-

TABLE 10.26
Selected examples of the oxidation of alcohols with TPA-RuO₄

Alcohol	Reaction conditions	Product	% yield
<i>n</i> -BuOH	10.6.20.A/1 h	<i>n</i> -PrCHO	95
<i>n</i> -C ₈ H ₁₇ OH	10.6.21/1 h	<i>n</i> -C ₇ H ₁₅ CHO	86
cyclo-C ₄ H ₇ OH	10.6.20.A/1 h	cyclobutanone	95
cyclo-C ₆ H ₁₁ OH	10.6.21/20 min	cyclohexanone	92
PhCH ₂ OH	10.6.20.A/2 h	PhCHO	80
	10.6.21/30 min	PhCHO	98
2-ClC ₆ H ₄ CH ₂ OH	10.6.20.A/4 h	2-ClC ₆ H ₄ CHO	81
4-MeOC ₆ H ₄ CH ₂ OH	10.6.20.A/12 h	4-MeOC ₆ H ₄ CHO	68
3,4-(MeO) ₂ C ₆ H ₃ CH ₂ OH	10.6.20/1.5 h	3,4-(MeO) ₂ C ₆ H ₃ CHO	98
Me ₂ C=CH(CH ₃) ₂ OH	10.6.21/40 min	Me ₂ C=CH(CH ₃)CHO	99
PhCH=CHCH ₂ OH	10.6.20.A/3 h	PhCH=CHCHO	90
	10.6.21/30 min	PhCH=CHCHO	97
BrCH=CMcCH ₂ OH	10.6.20.B/2.5 h	BrCH=CMcCHO	94
CH=CHMeCH ₂ OH	10.6.20.B/1 h	CH=CHMeCHO	82
CHMe(CH ₂) ₃ OH		CHMe(CH ₂) ₄ CHO	
ClCH ₂ CHOHCH ₂ OBz	10.6.20.B	ClCH ₂ CO.CH ₂ OBz	70
BzO(CH ₂) ₃ OH	10.6.20.B/30 min	BzO(CH ₂) ₂ CHO	85
XOCH ₂ CHMeCH ₂ OH ^a	10.6.20.B/20 min	XOCH ₂ CHMeCHO ^a	85
2-Hydroxymethyltetrahydro-furan-5-one	10.6.20.B/30 min	2-Formyltetrahydro-furan-5-one	52
(±)-Menthol	10.6.20.A/1 h	(±)-Menthone	85
(+)-Menthol	10.6.20.A/30 min	(+)-Menthone	90
<i>endo</i> -Norbornol	10.6.20.A/20 min	Bicyclo[2.2.1]heptan-2-one	73
Lanost-8-en-3β-ol	10.6.20.A/1.5 h	Lanost-8-en-3-one	81

^a X = *t*-butyldiphenylsilyl.

tion, the mixture is diluted with CH₂Cl₂ (50 ml), washed with aqueous Na₂SO₃ (sat. soln, 10 ml) and brine (10 ml), dried (MgSO₄), and evaporated to give the carbonyl compound.

Method B: Solid TPA-RuO₄ (50 mmol) is added in one portion* at room temperature to the substrate (1 mmol), *N*-methylmorpholine-*N*-oxide (1.5 mmol) and powdered 4Å molecular sieves (0.5 g) in CH₂Cl₂† (2 ml) under argon. When the substrate has been consumed, the mixture is chromatographed from silica to yield the carbonyl compound (*on larger scale, the perruthenate should be added portionwise with cooling; † where the reaction does not go to completion, MeCN can be added as a co-solvent).

Method C: The alcohol (2 mmol) and Adogen (53 mg, 0.15 mmol) in CH₂Cl₂ (15 ml) are stirred with K₂RuO₄ (0.1 g, 0.4 mmol) and K₂S₂O₈ (0.5 g, 8 mmol) in aqueous KOH (10%, 5 ml) at room temperature. The reaction is monitored by TLC analysis and, when complete (*ca.* 2–3 h), the aqueous phase is separated and extracted with CH₂Cl₂ (10 ml). The combined organic solutions are washed with H₂O (10 ml), dried (MgSO₄), and evaporated to give the carbonyl derivatives.

The protocol for the oxidation of alcohols (10.6.20) has been improved by the use of molecular oxygen as the oxidant in the presence of a catalytic amount of the perruthenate catalyst (10.6.21). Yields are extremely high with relatively short

reaction times [39]. In addition, polymer-supported perruthenate has also been used for the conversion of alcohols into the corresponding aldehydes or ketones in high yields (10.6.22) [e.g. 40–43]. The high yields can be retained with short reaction times, when an excess of the polymer-supported perruthenate is used [41–43].

10.6.21 Perruthenate-catalysed oxidation of alcohols by dioxygen

Powdered 4Å molecular sieves (2 g) and TPA-RuO₄ (36 mg, 0.1 mmol) are added to the alcohol (10 mmol) in CH₂Cl₂ (40 ml) and the mixture is stirred at room temperature under a positive pressure of O₂. After *ca.* 30 min, the mixture is filtered through a short column of silica and the filtrate is evaporated to yield the aldehyde or ketone.

10.6.22 Polymer-supported perruthenate oxidation of alcohols

The alcohol (0.5 mmol) is stirred with *N*-methylmorpholine *N*-oxide (88 mg, 0.75 mmol), 4Å molecular sieves (0.5 g) and polymer-supported perruthenate (0.1 g), prepared by adding KRuO₄ (10 mg, 1 mmol) to Amberlyst IR-27 resin (1 g), in CH₂Cl₂ or MeCN (5 ml) at room temperature until TLC analysis indicates complete consumption of the alcohol (*ca.* 16 h). The mixture is filtered and the filtrate evaporated to yield the carbonyl compound [e.g. PhCHO, >95% (16 h); PhCH=CHCHO, >95%; CH₂=CH(CH₂)₂CHO, 62%; *n*-C₇H₁₅CHO, 54%; cyclohexanone, 50%]. The resin can be reused without loss of activity.

The perruthenate oxidation of alcohols has been incorporated into a one-pot conversion of alkenes into carbonyl compounds via their initial hydroboration [44]. Overall yields can be as high as 98%. Where the initial alkene also contains carbonyl groups these are reduced in the first step and are reoxidized by the perruthenate.

10.6.23 One-pot conversion of alkenes into aldehydes and ketone

BH₃·Me₂S in *n*-C₆H₁₄ (2M, 0.33 mmol, 150 µl) is added by syringe to the alkene (1 mmol) in Et₂O (5 ml) at room temperature under Ar with stirring. The mixture is stirred for 3 h, then diluted with CH₂Cl₂ (3 ml), and crushed 4Å molecular sieves (0.1 g) and *N*-methylmorpholine-*N*-oxide (0.35 g, 3 mmol; 0.7 g 6 mmol when the alkene possesses a carbonyl group) are added. The mixture is stirred for a further 1 h and TPA-RuO₄ (17.6 mg, 0.05 mmol; 24.6 mg, 7 mmol when the alkene possesses a carbonyl group) is then added. When the solution becomes black (*ca.* 5 min), it is filtered through silica, which is subsequently washed with EtOAc, and the combined filtrate is stirred with activated charcoal, filtered, and evaporated to yield the carbonyl compound (98% cyclododecanone from cyclododecene; 84% cyclooctanone from cyclooctene; 61% formylcyclohexane from methylenecyclohexane; 50% 2-methylcyclohexanone from 1-methylcyclohexene; 72% decanal from dec-1-ene).

Tetra-*n*-propylammonium perruthenate also oxidizes sulphides to sulphones [45]. Yields are generally high for dialkyl sulphides and alkyl aryl sulphides, but lower for diaryl sulphides.

10.6.24 Oxidation of sulphides to sulphones

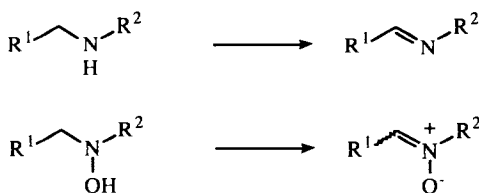
TPA-RuO₄ (18 mg, 0.05 mmol) is added with stirring at room temperature under N₂ to the sulphide (1 mmol), *N*-methylmorpholine-*N*-oxide (0.35 g, 3 mmol), and powdered 4Å molecular sieves (0.1 g) in MeCN (5 ml). The mixture is stirred at 40°C for a further 2–3 h, cooled, and the MeCN removed under vacuum. Chromatography of the residue on silica gives the sulphone [e.g. PhSO₂Me, 97%; Ph₂SO₂, 61%; (PhCH₂)₂SO₂, 90%; (CH₃)₄SO₂, 92%].

Secondary nitro compounds are oxidized to the corresponding ketones in moderate yields by a catalytic amount of tetra-*n*-propylammonium perruthenate in the presence of *N*-methylmorpholine-*N*-oxide and a silver salt [46]. Oxidation with a stoichiometric amount of the ammonium perruthenate has also been reported [47].

10.6.25 Conversion of secondary nitro compounds into ketones

TPA-RuO₄ (4.5 mg, 0.013 mmol) is added to the nitro compound (0.13 mmol), *N*-methylmorpholine-*N*-oxide (22.7 mg, 0.194 mmol), AgOAc (43 mg, 0.258 mmol), K₂CO₃ (90 mg, 0.65 mmol) and powdered 4Å molecular sieves (0.1 g) in MeCN (2 ml). The mixture is stirred for 10 h at 40°C and Et₂O (5 ml) is then added. Filtration through Celite and evaporation of the filtrate yields the ketone.

Secondary amines and *N,N*-dialkylhydroxylamines are rapidly oxidized by tetra-*n*-propylammonium perruthenate to imines and nitrones, respectively (Scheme 10.5) [48, 49]. Chiral centres are unaffected during the oxidation.



Scheme 10.5

10.6.26 Perruthenate oxidation of secondary amines (Table 10.27)

The amine (0.5 mmol), *N*-methylmorpholine-*N*-oxide (0.09 g, 0.75 mmol), TPA-RuO₄ (9 mg, 0.025 mmol) and powdered 4Å molecular sieves (250 mg) in dry MeCN (2.5 ml) are stirred under N₂ until the amine has been consumed. The solvent is then evaporated and the residue is chromatographed through Celite.

10.6.27 Perruthenate oxidation of *N,N*-dialkylhydroxylamines (Table 10.28)

The hydroxylamine (0.5 mmol), *N*-methylmorpholine-*N*-oxide (0.09 g, 0.75 mmol), TPA-RuO₄ (9 mg, 0.025 mmol) and powdered 4Å molecular sieves (250 mg) in dry MeCN

TABLE 10.27
Conversion of secondary amines into imines

R ¹ R ² NH	Reaction time	Product	% yield
R ¹ = Ph R ² = PhCH ₂	24 h	PhCH=NCH ₂ Ph	88
Ph Ph	20 h	PhCH=NPh	93
Ph CMe ₃	20 h	PhCH=NCMe ₃	62
1,2,3,4-Tetrahydroisoquinoline	72 h	3,4-Dihydroisoquinoline	73
1,2,3,4-Tetrahydroquinoline	24 h	3,4-Dihydroquinoline	52 ^a
2,3-Dihydroindole	6 h	Indole	73

^a + 32% quinoline.

TABLE 10.28
Selected examples of the conversion of hydroxylamines into nitrones

R ¹ R ² NOH	Reaction time	Product	% yield
R ¹ = Me R ² = Et	0.5 h	MeCH=N ⁺ O ⁻ .Et	100 ^a
Ph PhCH ₂	3 h	PhCH=N ⁺ O ⁻ .CH ₂ Ph	100 ^b
-(CH ₂) ₄ -	0.5 h	1-Pyrroline-1-oxide	100
-(CH ₂) ₅ -	3.5 h	1,2,3,4-Tetrahydropyridine-1-oxide	79
-(CH ₂) ₄ CHMe-	0.5 h	3,4,5,6-Tetrahydro-2-methylpyridine-1-oxide	83 ^c

^a Z:E ratio 1 : 50; increasing to 1 : 5 with longer reaction times. ^b Z:E ratio >50 : 1. ^c + 27% 2,3,4,5-tetrahydro-2-methylpyridine-1-oxide.

(2.5 ml) are stirred under N₂ for *ca.* 30 min. The solvent is then evaporated and the residue is chromatographed through Celite to yield the nitrone.

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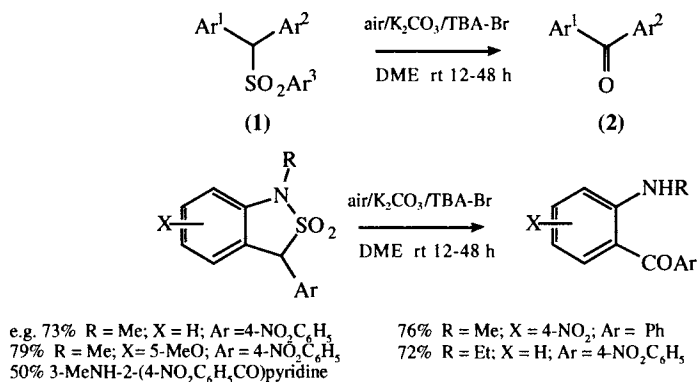
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10.7 AUTOXIDATION REACTIONS AND OXIDATION WITH HYDROGEN PEROXIDE

Benzoisothiazole-2,2-dioxides undergo autoxidation under basic conditions in the presence of TBA-Br to yield 2-arylaniline derivatives (Scheme 10.6) and the more simple diarylmethylsulphones produce diaryl ketones (Table 10.29) [1].

10.7.1 Autoxidation of diarylmethyl sulphones

The sulphone (1 mmol), TBA-Br (0.32 g, 0.1 mmol) and K₂CO₃ (2.0 g) in MeO-(CH₂)₂OMe (10 ml) are stirred in contact with air until all of the material has dissolved. The solution is filtered through Celite directly into CH₂Cl₂ (30 ml). The dried (MgSO₄) solution is evaporated to yield the benzophenone.



Scheme 10.6

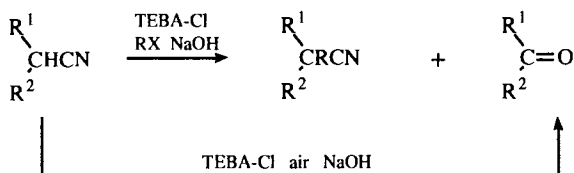
TABLE 10.29

Autoxidation of diarylmethyl sulphones to yield diarylketones

Ar ¹ Ar ² CHSO ₂ Ar ³			% yield Ar ¹ COAr ²
Ar ¹ = 4-O ₂ NC ₆ H ₅	Ar ² = Ph	Ar ³ = 4-MeC ₆ H ₅	87
4-O ₂ NC ₆ H ₅	4-MeOC ₆ H ₅	Ph	86
4-O ₂ NC ₆ H ₅	Thien-2-yl	Ph	80
Ph	5-Nitrothien-2-yl	Ph	67

Autoxidation of secondary acetonitriles under phase-transfer catalytic conditions [2] avoids the use of hazardous and/or expensive materials required for the 'classical' conversion of the nitriles into ketones. In the course of C-alkylation of secondary acetonitriles (see Chapter 6), it had been noted that oxidative cleavage of the nitrile group frequently occurred (Scheme 10.7) [3]. In both cases, oxidation of the anionic intermediate presumably proceeds via the peroxy derivative with the extrusion of the cyanate ion [2]. Advantage of the direct oxidation reaction has been made in the synthesis of aryl ketones [3], particularly of benzoylheteroarenes. The cyanomethylheteroarenes, obtained by a photochemically induced reaction of halo-heteroarenes with phenylacetonitrile, are oxidized by air under the basic conditions. Oxidative coupling of bromoacetonitriles under basic catalytic conditions has been also observed (see Chapter 6).

In contrast, nitriles are hydrolysed by hydrogen peroxide under basic catalytic conditions to produce the corresponding amides (~90%) [4].



Scheme 10.7

10.7.2 Oxidative cleavage of secondary acetonitriles to ketones (Table 10.30)

Method A: TEBA-Cl (0.25 g, 1.1 mmol) and aqueous NaOH (50%, 2.5 ml) in DMSO (15 ml) are added to the nitrile (0.025 mol) in DMSO (5 ml). O₂ is passed through the mixture and the temperature rises to *ca.* 50 °C spontaneously and a white precipitate is formed. The mixture is poured into H₂O (80 ml) and extracted with Et₂O (3 × 10 ml). The organic phase is separated, washed well with H₂O until the washings are neutral, dried (MgSO₄), and evaporated to yield the ketone.

Method B: The nitrile (1.3 mmol), aqueous NaOH (50%, 0.3 ml), TEBA-Cl (0.04 g, 0.2 mmol) and PhMe (6 ml) are stirred in an open vessel. Et₂O (250 ml) is added and the organic phase is separated, washed well with H₂O until the washings are neutral, dried (MgSO₄), and evaporated to give the ketone.

The autoxidation of cyclic ketones with dirhenium decacarbonyl under basic catalytic conditions produces dicarboxylic acids (68–73%); bicyclic ketones are converted into keto carboxylic acids and, when one ring is aromatic, quinones are obtained, e.g. 1-tetralone produces 2-hydroxy-1,4-naphthaquinone (93%), and HO₂C(CH₂)₄CO(CH₂)₃CO₂H (85%) is obtained from 1-decalone via a cyclic triketone [5].

TABLE 10.30

Selected examples of the oxidative cleavage of secondary acetonitriles to ketones

R ¹ CHR ² CN		Reaction conditions	% yield
R ¹ = Ph	R ² = Me	10.7.2.A/5 h	63
Ph	Ph	10.7.2.A/30 min	90 ^a
Ph	cyclo-C ₆ H ₁₁	10.7.2.A/3 h	84
Ph	Me ₂ N(CH ₂) ₂	10.7.2.A/3 h	63 ^b
Me	1-Naphthyl	10.7.2.A/3 h	91
<i>i</i> -Pr	1-Naphthyl	10.7.2.A/6 h	57
Ph	2-Pyridyl	10.7.2.B/3 h	99
Me	2-Pyridyl	10.7.2.B/48 h	45
<i>i</i> -Pr	2-Pyridyl	10.7.2.B/24 h	55
Ph	6-Methyl-2-pyridyl	10.7.2.A/1.5 h	86
Ph	6-Bromo-2-pyridyl	10.7.2.B/3 h	95
Ph	6-Chloro-2-pyridyl	10.7.2.B/3 h	96
Ph	6-(α -Cyanobenzyl)-2-pyridyl	10.7.2.B/3 h	99 ^c
Ph	3-Pyridyl	10.7.2.B/3 h	99
Ph	4-Pyridyl	10.7.2.B/3 h	97
Ph	2-Quinoliny	10.7.2.B/3 h	91
Ph	3-Quinoliny	10.7.2.B/3 h	92
Ph	2-Pyrazinyl	10.7.2.B/3 h	93
Ph	2-Pyrimidinyl	10.7.2.B/10 h	98

^a 99% PhCOPh from PhC(=NOH)Ph using 10.7.2.B (3 h). ^b Reaction temperature kept below 10 °C. ^c 2,6-dibenzoylpyridine.

10.7.3 Autoxidation of cyclic ketones

O₂ is bubbled through a mixture of the ketone (10 mmol), powdered KOH (2.24 g), K₂CO₃ (5.53 g), Rh₂(CO)₁₀ (48 mg, 0.1 mmol) and TEBA-Cl (0.07 g, 0.3 mmol) in MeO(CH₂)₂OMe (20 ml) until the ketone has been consumed. The mixture is cooled to 0°C, made acidic (pH 4) with HCl (10M), and extracted with Et₂O (3 × 50 ml). The dried (MgSO₄) ethereal extracts are evaporated to yield the oxidized products.

Benzophenones are produced by the oxidation of diarylmethanes under basic conditions [6–9]. The initial step requires a strongly basic medium to ionize the methane and the more lipophilic quaternary ammonium catalysts are preferred (Aliquat and tetra-*n*-octylammonium bromide are better catalysts than tetra-*n*-butylammonium bromide). The oxidation and oxidative dehydrogenation of partially reduced arenes to oxo derivatives in a manner similar to that used for the oxidation of diarylmethanes has been reported, e.g. fluorene is converted into fluorenone (100%), and 9,10-dihydroanthracene and 1,4,4a,9a-tetrahydroanthraquinone into anthraquinone (75% and 100%, respectively) [6].

10.7.4 Oxidation of diarylmethanes to benzophenones

Method A: Aliquat (0.02 mol) and the diarylmethane (0.1 mol) in PhMe (30 ml) are added to aqueous NaOH (50%, 50 ml) in a stainless-steel Parr bomb under O₂ at 200 psi. The mixture is stirred at 40–50°C for 18–22 h. H₂O (100 ml) and CH₂Cl₂ (100 ml) are added and the organic phase is separated, dried (MgSO₄), and evaporated to yield the benzophenone.

Method B: The substrate (9.6 mmol) and TEBA-Cl (0.23 g, 1 mmol) in PhMe (10 ml) are stirred with aqueous NaOH (50%, 4 ml) at 25°C. O₂ is bubbled through the mixture until TLC analysis indicates the complete oxidation of the methylene group. The reaction mixture is then worked up as described in 10.7.4.A.

Epoxidation of α,β -unsaturated ketones by hydrogen peroxide or *t*-butyl peroxide is promoted by the addition of tetra-*n*-butylammonium fluoride [10], whereas the corresponding reaction with 1,4-disubstituted but-2-en-1,4-diones is catalysed by quaternary ammonium iodides [11]. Oxiranes are also produced by the catalysed reaction of *t*-butyl peroxide with α,β -unsaturated sulphonates under basic conditions [12].

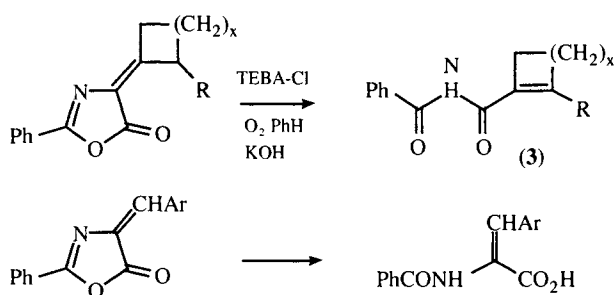
10.7.5 Epoxidation of α,β -unsaturated ketones and but-2-en-1,4-diones

Method A: TBA-F in THF (1M, 1 ml, 1 mmol) is added to the α,β -unsaturated ketone (1 mmol) and aqueous H₂O₂ (30%, 0.17 ml, 1.5 mmol) in DMSO (1 ml) at room temperature and the solution is stirred for ca. 6 h. H₂O (15 ml) is added and the solution is extracted with Et₂O (3 × 10 ml). The extracts are washed well with brine and evaporated to give the oxirane (60–95%).

Method B: Aqueous H₂O₂ (30%, 0.6–4.0 ml) in THF (3 ml) is added dropwise to the but-2-en-1,4-dione (1 mmol) and TBA-I or TMBA-I (0.1 mmol) in THF (10 ml) at 0°C. The

mixture is stirred for 20–96 h and then poured into aqueous KI (5M, 5 ml). Aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (0.5 M) is added and the solution extracted with EtOAc (3×25 ml). The extracts are washed well with $\text{Na}_2\text{S}_2\text{O}_3$ and brine, dried (MgSO_4), and evaporated to yield the oxirane (~55%).

The autoxidation of azlactones under basic conditions provides a convenient route to diacylamines [13]. Yields are usually >80%, except for the benzylidene derivatives, which are hydrolysed to the acylaminoacetic acids (Scheme 10.8).



Scheme 10.8

10.7.6 Autoxidation of azlactones to diacylamines

O_2 is passed through a solution of the azlactone (10 mmol), powdered KOH (0.56 g, 10 mmol) and TEBA-Cl (12 mg, 1 mmol) in PhH (80 ml) at 28°C for *ca.* 5 h. When the azlactone has been consumed, as shown by TLC analysis, the PhH solution is washed well with H_2O , dried (MgSO_4), and evaporated to yield the amide (e.g. (3)): $x = 3$, $\text{R} = \text{H}$, 90%; $x = 3$, $\text{R} = \text{Me}$, 80%; $x = 2$, $\text{R} = \text{H}$, 75%.

The metal-catalysed autoxidation of alkenes to produce ketones (Wacker reaction) is promoted by the presence of quaternary ammonium salts [14]. For example, using copper(II) chloride and palladium(II) chloride in benzene in the presence of cetyltrimethylammonium bromide, 1-decene is converted into 2-decanone (73%), 1,7-octadiene into 2,7-octadione (77%) and vinylcyclohexane into cyclohexylethanone (22%). Benzyltriethylammonium chloride and tetra-*n*-butylammonium hydrogen sulphate are ineffective catalysts. It has been suggested that the process is not micellar, although the catalysts have the characteristics of those which produce micelles. The Wacker reaction is also catalysed by rhodium and ruthenium salts in the presence of a quaternary ammonium salt. Generally, however, the yields are lower than those obtained using the palladium catalyst and, frequently, several oxidation products are obtained from each reaction [15].

Photochemical oxidation of electron-rich alkenes with the simultaneous reduction of the initially formed peroxide with tetra-*n*-butylammonium borohydride to the hydroxy compound has been reported, but the procedure has not been shown to be generally useful [16].

Many of the metal-promoted oxidations of alcohols with hydrogen peroxide in the presence of a phase-transfer catalyst have limited preparative value, as they use high concentrations of hydrogen peroxide or have high catalyst:substrate ratios [17]. However, the procedure can be optimized using 30% hydrogen peroxide at 80°C with ruthenium chloride in the presence of a quaternary ammonium catalyst [18]; primary aliphatic alcohols are oxidized to carboxylic acids, primary benzylic alcohols produce the corresponding benzaldehydes or, after longer reaction periods, the benzoic acids, and secondary alcohols are oxidized to ketones. Using an analogous protocol, styrene is oxidatively cleaved to benzaldehyde (60%) with lesser amounts of benzoic acid and styrene oxide; when palladium chloride–Aliquat is used, the major product is acetophenone (56%) with benzaldehyde (12%) and benzoic acid (14%) [19].

10.7.7 Peroxide oxidation of primary and secondary alcohols (Table 10.31)

H₂O₂ (30%, 15 ml, 130 mmol) is fed at a constant rate of *ca.* 0.3 ml/min using a syringe pump into the alcohol (48 mmol), hydrated RuCl₃ (0.02 g, 0.077 mmol) and DDDMA-Br (0.4 g, 1 mmol). The organic phase is separated and evaporated. The crude products are purified by chromatography from silica.

TABLE 10.31

Selected examples of the ruthenium-catalysed oxidation of primary and secondary alcohols

Alcohol	Reaction time	Oxidation product	% yield
Me(CH ₂) ₅ OH	45 min	Me(CH ₂) ₄ CO ₂ H	85 ^a
Me(CH ₂) ₆ OH	45 min	Me(CH ₂) ₅ CO ₂ H	89 ^a
Me(CH ₂) ₇ OH	45 min	Me(CH ₂) ₆ CO ₂ H	85 ^a
Me(CH ₂) ₈ OH	45 min	Me(CH ₂) ₈ CO ₂ H	87 ^a
PhCH ₂ OH	45 min	PhCHO	91 ^b
4-MeC ₆ H ₄ CH ₂ OH	45 min	4-MeC ₆ H ₄ CHO	86
4-O ₂ NC ₆ H ₄ CH ₂ OH	45 min	4-O ₂ NC ₆ H ₄ CHO	80
4-BrC ₆ H ₄ CH ₂ OH	45 min	4-BrC ₆ H ₄ CHO	45
PhCHOHMe	1.5 h	PhCOMe	90
Me(CH ₂) ₆ CHOHMe	1.5 h	Me(CH ₂) ₆ COMe	82
cyclo-C ₆ H ₁₁ OH	1.5 h	cyclohexanone	90

^a + *ca.* 5–10% aldehyde and 10–15%. ^b 95% PhCO₂H after 1.5 h.

Tungsten-catalysed oxidation of alcohols by hydrogen peroxide is achieved in high yield in the presence of tetra-*n*-butylammonium hydrogen sulphate [20–22]. Secondary alcohols are converted into ketones (>90%) [e.g. 21], but primary alcohols generally are oxidized completely to the carboxylic acids [21]. Aldehydes are also oxidized to the carboxylic acids [e.g. 21]. In contrast, using procedure **10.7.8.B**, which is adaptable to scale up, benzyl alcohols are converted into the aldehydes; benzoic acids are only formed with an excess of hydrogen peroxide [22].

10.7.8 Tungsten(VI)-promoted oxidation of alcohols

Method A: $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (0.33 g, 1 mmol) and H_2SO_4 (10–20 mmol sufficient to adjust the pH of the medium to between 1.4 and 3.0) are added to the alcohol (10 mmol), H_2O_2 (70%, 1 ml) and Aliquat (0.8 g, 2 mmol) in $\text{Cl}(\text{CH}_2)_2\text{Cl}$ (10 ml). When all of the oxidant has been consumed (30–200 min), the organic phase is separated, dried (MgSO_4), and evaporated to yield the carbonyl compound.

Method B: H_2O_2 (5%, 50 ml, 73.5 mmol) is added at room temperature to $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (4.77 g, 14.5 mmol) and MTOA- HSO_4 (6.74 g, 14.5 mmol) and the mixture is stirred for 10 min. The alcohol (0.75 mmol) in PhMe (150 ml) is then added and the mixture is heated at 70°C for 10 min. H_2O_2 (30%, 113 ml, 1. mol) is added dropwise over a period of 5 h while the temperature is kept at <75°C. The mixture is cooled to room temperature, and the organic phase is separated, washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (sat. soln, 50 ml), dried (Na_2SO_4), and fractionally distilled to yield the aldehyde (e.g. 87% PhCHO; 90% 4-MeOC₆H₄CHO; 91% 4-MeC₆H₄CHO, 81% 4-BrC₆H₄CHO; 82% 4-ClC₆H₄CHO; 59% 4-O₂NC₆H₄CHO).

Cyclic allyl peroxides are converted stereoselectively into the dihydroxypropyl peroxides using a modified Sharpless procedure with osmium tetroxide and *t*-butyl peroxide in the presence of benzyltrimethylammonium acetate [23]. Yields are generally good with exclusive *anti*-addition with respect to the peroxy group, although both the stereoselectivity and yield (<40%) are poor for the oxidation of 2,3-dihydrofuran-3-yl peroxide and 2,3-dihydro-4*H*-pyran-4-yl peroxide.

10.7.9 Stereoselective bishydroxylation of cyclic allyl peroxides

The allyl peroxide (1 mmol) and *t*-BuO₂H (0.135 g, 1.5 mmol) are added to TMBA-OAc (0.1 g, 0.5 mmol) in Me₂CO (4 ml) and the mixture is cooled to 0°C. OsO₄ solution (0.1 ml), prepared from OsO₄ (20 mg) and *t*-BuO₂H (0.02 ml) in *t*-BuOH (4 ml), is added and the mixture is stirred at 0°C for 1 h and then for further 10 h at room temperature. Et₂O (10 ml) and aqueous Na₂SO₃ (10%, 10 ml) are added at 0°C and the mixture is stirred at room temperature for 1 h. The mixture is saturated with NaCl and the organic phase is separated. The aqueous phase is extracted with Et₂O (5 × 15 ml) and the combined ethereal solutions are washed well with brine, dried (MgSO_4), and evaporated to yield the diol (e.g. 73% from *t*-butyl cyclopenten-3-yl peroxide; 70% from *t*-butyl cyclohexen-3-yl peroxide; 58% from *t*-butyl 2,5-dihydrofuran-2-yl peroxide; 61% from *t*-butyl 5,6-dihydro-2*H*-pyran-2-yl peroxide).

It has been shown that a stoichiometric reaction with benzene selenic anhydride in the absence of a phase-transfer catalyst can be used for the oxidation of hydroquinones to quinones, but such an oxidizing agent is expensive, compared with, for example, phase-transfer catalysed hypochlorite oxidation methods (see Section 10.4). The active selenium agent can be regenerated *in situ*, but such mixtures can be hazardous. A more convenient, safe and relatively cheap procedure, that can be used on a large-scale, utilizes benzene diselenide in the presence of hydrogen peroxide and a phase-transfer catalyst [24]; a selenium-based oxidizing agent, thought to be a

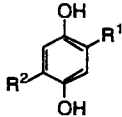
peroxyselenic acid, is initially generated. In the absence of the quaternary ammonium catalyst, the reaction is slow. Yields tend to be good, except with electron-deficient hydroquinones, and maximum conversion is attained, when the oxidation is conducted in sequential batches.

10.7.10 Selenium–hydrogen peroxide oxidation of hydroquinones (Table 10.32)

(PhSe)₂ (0.8 g, 2.5 mmol) and TBA-HSO₄ (0.11 g, 0.33 mmol) are dissolved in CH₂Cl₂ (500 ml) and added to H₂O₂ (30%, 180 ml). The mixture is stirred at room temperature until the yellow colour disappears. The hydroquinone (0.27 mol) is then added and the mixture is stirred for *ca.* 1 h (the reaction is exothermic and may reflux). When the reaction has subsided, a further volume of the premixed oxidizing agent [(PhSe)₂ (0.22 g, 0.7 mmol), H₂O₂ (30%, 1.9 ml) and TBA-HSO₄ (22 mg, 0.06 mmol) in CH₂Cl₂ (17 ml)] is added, followed by hydroquinone (0.27 mol). The mixture is stirred for a further 1 h and the process is repeated with a further portion of the oxidizing mixture (as above) and the hydroquinone (0.27 mol). The mixture is stirred for a further 1 h and the CH₂Cl₂ solution is then separated, washed with aqueous NaHCO₃ (sat. soln, 3 × 100 ml) and H₂O (3 × 200 ml), dried (MgSO₄), and evaporated to yield the quinone.

This procedure can be scaled up to kg scale, but care should be taken as the exothermic reaction becomes vigorous.

TABLE 10.32
Selenium–hydrogen peroxide oxidation of hydroquinones

		Method	% yield of quinone
R ¹ = Me	R ² = H	10.7.10	82
<i>t</i> -Bu	H	10.7.10	88
<i>t</i> -Bu	<i>t</i> -Bu	10.7.10	81
Cl	H	10.7.10	64
MeO	H	10.7.10	90 ^a

^aAlso obtained (62%) from the oxidation of vanillin via a Baeyer–Villiger oxidation of the formyl group.

Bulky quaternary ammonium salts promote the ruthenium-catalysed oxidation of anilines by hydrogen peroxide to nitrobenzenes [25]. In the absence of the ammonium salt, the major product is the azoxybenzene, whereas lower molecular weight tetra-alkylammonium salts produce a mixture of products.

10.7.11 Ruthenium-catalysed oxidation of anilines

The aniline (54 mmol) and Aliquat or DDDMA-Br (3 mmol), and RuCl₃ (16 mg, 0.077 mmol) in 1,2-dichlorobenzene (10 ml) are stirred at 90°C for 10 min and H₂O₂

(30%, 60 ml) is then added. The mixture is refluxed for 24 h and the aqueous phase is then separated and extracted with CH_2Cl_2 (2×15 ml). The combined organic solutions are dried (Na_2SO_4) and evaporated to yield the oxidized products [e.g. PhNH_2 gives PhNO_2 (60%) and PhN(O)=NPh (15%) using DDDMA-Br ; 55% and 25% with Aliquat].

Terminal alkynes have been effectively oxidized to keto aldehydes by hydrogen peroxide in the presence of Adogen, mercury(II) acetate and a molybdate salt [26]. Tungstate salts tend to oxidize the system to the carboxylic acid with cleavage of the triple bond. The reaction, which presumably proceeds via molybdenum(VI) and tungsten(VI) peroxo complexes, has no effect on internal alkynes. In contrast, alkenes are converted either into oxiranes (>75%) or diols (70–80%) by the tungsten(VI)-promoted reaction with hydrogen peroxide [27–31]. Procedure **10.7.13.B** obviates the need for chlorinated solvents and is suitable for the large-scale preparation of the oxiranes; the modified procedure (**10.7.14**) also provides a valuable route to water-soluble diols via the initial formation of the acid-labile oxiranes.

10.7.12 Oxidation of alk-1-ynes to 2-oxo aldehydes

The pH of an aqueous solution of $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$ (0.15 mmol in 1 ml H_2O) is adjusted to 0.9–4.6 with conc. H_2SO_4 and added to the alkyne (6.1 mmol), $\text{Hg}(\text{OAc})_2$ (1.6 or 0.8 mmol), and Adogen (0.27 g, 0.6 mmol) at 20°C. H_2O_2 (70%, 1 ml, 20.5 mmol) is added and the mixture is stirred for *ca.* 1 h and then directly chromatographed to yield the oxo aldehydes and unchanged starting material [e.g. $\text{PhC}\equiv\text{CH}$ yields PhCOCHO (26–32% at pH 1.1, 28–43% at pH 2.6, 37% at pH 4.6); *n*- $\text{BuC}\equiv\text{CH}$ yields *n*- BuCOCHO (20–29% at pH 1.1)]. The corresponding reactions with sodium tungstate yields PhCO_2H (93%) and *n*- BuCO_2H (55%).

10.7.13 Tungsten(VI)-promoted epoxidation of alkenes (Table 10.33)

Method A: The pH of a solution of powdered $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (1.65 g, 5 mmol) in aqueous H_3PO_4 (40%, 2.45 ml) and H_2O_2 (85%, 51 g) is adjusted 1.6 by the addition of H_2SO_4 (30%). The alkene (0.2 mol) and Aliquat (0.82 g, 2 mmol) in $\text{Cl}(\text{CH}_2)_2\text{Cl}$ (15 ml) are added. The mixture is stirred at 70°C for *ca.* 45 min and the organic phase is then separated, washed well with H_2O , and evaporated to yield the oxirane.

Method B: The alkene (0.59 mol) is added with stirring at room temperature to $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (3.919 g, 11.9 mmol), $\text{H}_2\text{NCH}_2\text{PO}_3\text{H}_2$ (0.66 g) and MTOA-HSO_4 (2.77 g, 5.94 mmol) in aqueous H_2O_2 (30%, 0.67 ml, 5.94 mmol). The mixture is stirred for 2 h at 90°C and then cooled to room temperature. The organic phase is separated, washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (sat. soln, 150 ml), and fractionally distilled to yield the oxirane.

Method C: MTOA-HWO_4 (0.86 g, 1.4 mmol) and PhPO_3H_2 (0.44 g, 2.8 mmol) are added to the alkene (0.12 mol) and H_2O_2 (70%, 1.2 ml) in dioxane (5 ml) and the mixture is stirred at 70°C until the reaction is complete, as shown by GLC analysis. The oxirane is isolated as described in **10.7.13.A** [e.g. 100% from cyclo- C_6H_{10} (48 min); 70% from *n*- $\text{C}_8\text{H}_{17}\text{CH=CH}_2$ (4 h); 80% from PhCH=CH_2 (4 h)].

Method D: The alkene (2 mmol) and H_2O_2 (30%, 1 ml) are added with stirring to $(\text{TBA})_2\text{-W}_2\text{O}_{11}$ (0.16 g, 0.2 mmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (2 ml) at 30–50°C for 15–45 h. CH_2Cl_2 (10 ml) and H_2O (5 ml) are then added and the organic phase is separated, dried (MgSO_4), and fractionally distilled to yield the oxirane.

TABLE 10.33

Selected examples of the tungsten(VI) promoted epoxidation of alkenes by hydrogen peroxide

Alkene	Reaction conditions	% yield of oxirane
$n\text{-C}_6\text{H}_{13}\text{CH=CH}_2$	10.7.13.B /90° C/0.2 h	89
$n\text{-C}_{10}\text{H}_{21}\text{CH=CH}_2$	10.7.13.B /90° C/2 h	93
$\text{CH}_2=\text{CHCH}_2\text{Cl}$	10.7.13.A /60° C/2.5 h ^a	80
PhCH=CH_2	10.7.13.A /40° C/3 h ^b	77
cyclo- C_6H_{10}	10.7.13.A /70° C/0.4 h ^b	88

^aAt pH 2. ^bAt pH 3.

10.7.14 Tungsten(VI)-promoted bishydroxylation of alkenes

(MTOA)₃-PO₄[WO(O₂)₂]₄ (1.8 g, 0.8 mmol) and the alkene (0.26 mol) in PhH (10 ml) are added to H₂O₂ (0.1 mmol) in H₂O (160 ml) and the pH is adjusted to 1.2 by the addition of aqueous H₂SO₄ (30%). The mixture is stirred under reflux for ca. 4 h and then cooled to room temperature. Aqueous H₂SO₄ (30%, 2 ml) is added to the separated aqueous phase, followed by solid Na₂S₂O₅ until KI-starch paper gives a negative result. The pH of the solution is adjusted to 8.0 by the addition of Na₂CO₃ and it is then evaporated under reduced pressure. The residue is taken up in Me₂CO (3 × 50 ml). The extracts are concentrated to half volume and extracted with Et₂O (50 ml). The dried (Na₂SO₄) ethereal extracts are evaporated to yield the diol [e.g. 82% from PhCH=CH₂; 83% from PhC(Me)=CH₂; 72% from Me₂C=CMe₂; 88% from cyclopentene; 86% from cyclohexene].

Cyclic enones can be oxidatively cleaved by a range of reagents to yield keto acids. As ozonolysis can be quite hazardous for large-scale preparations with the build up of ozonides, the procedure has been modified using quaternary ammonium salts to catalyse the transfer of peroxide anion for a rapid oxidative work-up [32]. Two methods are available but, in the safer procedure (**10.7.15.A**), there is no effective build-up of the ozonide.

10.7.15 Oxidative ozonolysis of enones (Table 10.34)

Method A: The enone (0.1 mol) in CH₂Cl₂ (200 ml) is added to aqueous H₂O₂ (30%, 15.5 ml) NaOH (5.1 g, 0.13 mol), and Adogen (0.2 g, 0.45 mmol). The mixture is cooled

TABLE 10.34

Selected examples of the oxidative conversion of enones into keto acids

Enone	Product	% yield ^a
3,5,5-Trimethylcyclohex-2-en-1-one	MeCOCH ₂ CMe ₂ CH ₂ CO ₂ H	92
3,6,6-Trimethylcyclohex-2-en-1-one	MeCO(CH ₂) ₂ CMe ₂ CO ₂ H	95
3-Methylcyclohex-2-en-1-one	MeCO(CH ₂) ₃ CO ₂ H	48 ^b
Progesterone	'A-ring opened keto acid'	84
Cholestanone	'A-ring opened keto acid'	85

^a Using procedure **10.7.15.A**. ^b Water soluble

to -5°C and O_3 is introduced over a period of 15–20 min until all of the enone has been consumed. The aqueous phase is separated and acidified with concentrated HCl to yield the keto acid.

Method B: Ozonolysis of the enone is conducted at -78°C and the H_2O_2 , NaOH and Adogen is then added. The products are isolated as described in **10.7.15.A**.

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10.8 MISCELLANEOUS OXIDATION REACTIONS

Freymy's salt, which is frequently employed in a wide range of oxidation reactions [1], has been shown to selectively oxidize benzylic alcohols in preference to saturated and allylic alcohols [2]. Yields are generally $>95\%$, except for 4-nitrobenzyl alcohol. Under the normal reaction conditions, saturated primary alcohols are not

oxidized but, over a prolonged reaction period, aldehydes can be isolated (Table 10.35). In competitive reactions benzylic alcohols are completely oxidized and allylic alcohols are recovered unchanged after 20 hours.

10.8.1 Preferential oxidation of benzylic alcohols with Fremy's salt

The alcohol (1 mmol) in PhH (5 ml) is added to aqueous Na_2CO_3 (5%, 30 ml), $(\text{KSO}_3)_2\text{NO}$ (0.8 g, 3 mmol) and Adogen (0.2 g, mmol). The mixture is stirred for *ca.* 12 h and the aqueous phase is then separated and extracted with PhH (3×10 ml). The combined PhH solutions are dried (MgSO_4) and evaporated to yield the carbonyl derivatives.

TABLE 10.35
Selected examples of the oxidation of alcohols with Fremy's salt

Alcohol	Reaction time	% yield	Alcohol	Reaction time	% yield
PhCH_2OH	12 h	90	PhCH(OH)Ph	12 h	93
4-MeC ₆ H ₄ CH ₂ OH	12 h	82	Fluorenol	12 h	91
4-MeOC ₆ H ₄ CH ₂ OH	12 h	86	MeCH(OH)CH=CH_2	48 h	65
4-O ₂ NC ₆ H ₄ CH ₂ OH	12 h	67	$\text{C}_8\text{H}_{11}\text{CH=CHCH}_2\text{OH}$	120 h	85
2-FurylCH ₂ OH	12 h	90	$\text{PhCH}_2\text{CH(OH)CH=CH}_2$	60 h	78
PhCHOHMe	12 h	90	cyclo-C ₆ H ₁₁ OH	48 h	68
PhCHOHEt	12 h	88	$\text{C}_{16}\text{H}_{33}\text{OH}$	120 h	87

Halogens are frequently used as oxidation agents and, under two-phase conditions, they can either be employed as ammonium complex halide salts [3], or in the molecular state with or without an added quaternary ammonium catalyst [4]. Stoichiometric amounts of tetra-*n*-butylammonium tribromide under pH controlled conditions oxidize primary alcohols and low-molecular-weight alkyl ethers to esters, α,ω -diols and cyclic ethers produce lactones [3], and secondary alcohols yield ketones. Benzoin is oxidized to the corresponding benzil (80–90%) by the tribromide salts in acetonitrile in the presence of benzoyl peroxide [5].

Benzene-1,4-diols are oxidized to quinones by benzyltrimethylammonium tribromide under mild conditions in almost quantitative yields [6]. With an excess of the tribromide further reaction produces the 2-bromo-1,4-quinones. This oxidation is in contrast to the analogous reaction of phenols, which produces bromophenols (see Section 2.3). Hindered 4-methyl-phenols are oxidized to the corresponding benzyl alcohols, benzaldehydes, bromomethyl derivatives and 4-bromo-4-methylcyclohexa-2,5-dien-1-ones [7]. Benzylic alcohols are oxidized under neutral or basic conditions to yield the corresponding aldehydes (>70%); oxidation with an excess of the reagent produces the benzoic acids (>90%) [8].

10.8.2 Oxidation of alcohols and ethers by TBA-Br₃ (Table 10.36)

Oxidation of primary alcohols and low molecular weight ethers: The alcohol (or ether) (10 mmol) and TMBA-Br₃ (4.29 g, 11 mmol) in CCl_4 (10 ml) are stirred with

TABLE 10.36
Selected examples of the oxidation of alcohols and ethers by TBA-Br₃^a

	Reaction conditions	Product	% yield
<i>Alcohols</i>			
EtOH	10.8.2/7 h	MeCO ₂ Et	11
<i>n</i> -PrOH	10.8.2/5.5 h	EtCO ₂ Pr	52
<i>n</i> -BuOH	10.8.2/4.5 h	<i>n</i> -PrCO ₂ Bu	55
<i>n</i> -C ₅ H ₁₁ OH	10.8.2/12 h	<i>n</i> -BuCO ₂ C ₅ H ₁₁	85
<i>n</i> -C ₆ H ₁₃ OH	10.8.2/12 h	<i>n</i> -C ₅ H ₁₁ CO ₂ C ₆ H ₁₃	96
<i>n</i> -C ₈ H ₁₇ OH	10.8.2/12 h	<i>n</i> -C ₇ H ₁₅ CO ₂ C ₈ H ₁₇	99
PhCH ₂ OH	10.8.2/15 h	PhCHO	89 ^b
Ph(CH ₂) ₂ OH	10.8.2/4 h	PhCH ₂ CO ₂ (CH ₂) ₂ Ph	23
HO(CH ₂) _n OH			
<i>n</i> = 4	10.8.2/5.5 h	γ-Butyrolactone	60
<i>n</i> = 5	10.8.2/2.5 h	δ-Valerolactone	49
<i>n</i> = 6	10.8.2/2.5 h	Mixture including polymeric ester	
<i>Ethers</i>			
[Me(CH ₂) ₂] ₂ O	10.8.2/3 h	MeCH ₂ CO ₂ (CH ₂) ₂ Me	33 ^c
[Me(CH ₂) ₅] ₂ O	10.8.2/5 h	Me(CH ₂) ₄ CO ₂ (CH ₂) ₅ Me	78 ^{c,d}
(PhCH ₂) ₂ O	10.8.2/12.5 h	PhCHO	63 ^c
Tetrahydrofuran	10.8.2/45 h	γ-Butyrolactone	55 ^c
Tetrahydropyran	10.8.2/10 h	δ-Valerolactone	13 ^c

^a 1 : 1 ratio of TBA-Br₃:substrate. ^b 89% PhCO₂H with 2 equivalents of TBA-Br₃. ^c 2 : 1 ratio of TBA-Br₃:substrate.

^d 90% with 4.4 : 1 ratio of TBA-Br₃:substrate.

Na₂HPO₄·12H₂O (9.31 g, 26 mmol) in H₂O (10 ml) at 60–70°C until the orange colour disappears. The mixture is cooled to room temperature and aqueous NaHSO₃ (20%, 10 ml) is added. The organic phase is separated, washed with H₂O (100 ml), dried (MgSO₄), and evaporated to yield the esters.

Oxidation of α,ω-diols and cyclic ethers: The diol (or ether) (10 mmol) and TBA-Br₃ (8.19 g, 21 mmol) in CCl₄ (10 ml) are stirred with Na₂HPO₄·12H₂O (16.4 g, 46 mmol) in H₂O (20 ml) at 70°C. The reaction mixture is cooled to room temperature and aqueous Na₂CO₃ (sat soln.) is added to make the solution alkaline, followed by aqueous NaHSO₃ (20%, 20 ml). The aqueous mixture is extracted with CH₂Cl₂ (4 × 10 ml) and Et₂O (50 ml) is added to the combined extracts, which are filtered, dried (MgSO₄), and evaporated to yield the lactone.

Oxidation of benzylic alcohols: TEBA-Br₃ (2.05 g, 5.25 mmol) and NaOH (0.6 g) in H₂O (25 ml) are added dropwise to the benzylic alcohol (5 mmol) in CCl₄ (25 ml) and the mixture is stirred at room temperature for ca. 15 h until the yellow colour fades. Aqueous NaHSO₃ (5%, 5 ml) is added and the aqueous phase is separated and extracted with CH₂Cl₂ (3 × 30 ml). The dried (MgSO₄) organic phases are evaporated to yield the aldehyde.

10.8.3 Oxidation of benzene-1,4-diols with TBA-Br₃

Method A: Aqueous AcONa (15%, 20 ml) is added to the diol (2 mmol) and TMBA-Br₃ (0.86 g, 2.2 mmol) in CH₂Cl₂ (10 ml) and the solution is stirred at room temperature for

2–5 min until the colour is discharged. The organic phase is then separated, washed well with H_2O , dried (MgSO_4), and evaporated to yield the quinone.

Method B: TMBA- Br_3 (4.68 g, 12 mmol) is added to the diol (2 mmol) in AcOH (5 ml) and H_2O (10 ml) and the solution is stirred at 60°C for 5 h. H_2O (10 ml) is added and the mixture is cooled to 0°C for precipitation of the bromoquinone.

Polymer-supported ammonium tribromides convert methyl and methylene ketones into the corresponding α -bromo ketones in yields varying from 55 to 75% (see Section 2.3) [9].

The stoichiometric reaction of sulphides with ammonium tribromides under basic conditions leads to sulfoxides [10]. In a modified procedure, oxidation in ^{18}O -enriched water produces the ^{18}O -labelled sulfoxide [11].

10.8.4 Tribromide oxidation of sulphides

Method A: TMBA- Br_3 (4.68, 12 mmol) is added to the sulphide (10 mmol) in CH_2Cl_2 (30 ml) and aqueous NaOH (8%, 15 ml) and the mixture is stirred at room temperature for 1 h. When the mixture is completely decolourized, aqueous NaHSO_3 (20%, 10 ml) is added, and the organic phase is separated. The aqueous phase is extracted with CH_2Cl_2 (2×10 ml) and the combined organic solutions are dried (MgSO_4) and evaporated to yield the sulfoxide.

Method B: PTMA- Br_3 (0.39 g, 1.0 mmol) is added portionwise to the sulphide (1.0 mmol) in pyridine (1.8 ml) and ^{18}O -enriched H_2O (0.2 ml) at 0°C . The mixture is stirred at room temperature for *ca.* 1 h and is then poured into H_2SO_4 (2M, 25 ml) at 0°C . The precipitated ^{18}O -labelled sulfoxide is collected, washed well with H_2O , and dried.

Sulphides are oxidized to sulfoxides using catalytic amounts of gold(III) chloride or bromide and tetra-*n*-butylammonium salts in the presence of nitric acid, or the preformed complex salts [12–14]. Although selective, the procedure has little to commend it over other methods. Dialkyl sulphides are converted into the sulfoxides (>90%) within 2 hours, aryl alkyl sulphides require *ca.* 60 hours, and diaryl sulphides require a prohibitively long reaction time. Oxidation of di(alkylthio)alkanes, $\text{R}'\text{S}(\text{CH}_2)_n\text{SR}^2$, produces either the mono or disulfoxides, depending on the strength of the nitric acid used and the chain length. Using 10% nitric acid, the monosulfoxide is obtained, when $n = 1$, whereas the disulfoxide is formed when $n > 1$. With more dilute concentrations of nitric acid (5%), the monosulfoxide is formed when $n = 1$ –3 and mixtures of mono- and disulfoxides are produced for $n > 3$. Oxidation of non-symmetrical di(alkylthio)alkanes leads to the less hindered monosulfoxides [12–14].

Other more effective and cheaper phase-transfer procedures are available and, even a two-phase system with dilute nitric and sulphuric acids in the absence of a phase-transfer catalyst is reported to be as selective and more versatile than the gold(III) method [15].

10.8.5 Tetra-*n*-butylammonium tetrachloroaurate

HAuCl₄ (26.7 g, 78.6 mmol) in HCl (1 M, 200 ml) and TBA-Cl (4.17 g, 15 mmol) in CH₂Cl₂ (15 ml) are stirred for 1 h. The organic phase is separated, dried (Na₂SO₄), and evaporated to yield TBA-AuCl₄, m.p. 161–162°C.

10.8.6 Tetra-*n*-butylammonium tetrabromoaurate

TBA-Br (4.15 g, 13.2 mmol) in CH₂Cl₂ (200 ml) is added to HAuBr₄, obtained by the dissolution of gold (2.0 g) in aqueous HBr (48%, 60 ml) and HNO₃ (89%, 30 ml). The mixture is stirred for 10 min and the organic phase is then separated, washed well with H₂O, dried (Na₂SO₄), and evaporated to yield TBA-AuBr₄, m.p. 176–177°C.

10.8.7 Gold(III)-promoted oxidation of dialkyl sulphides

HNO₃ (10%, 16 ml, 25 mmol) and TBA-AuCl₄ or TBA-AuBr₄ (0.25 mmol) are added to the dialkyl sulphide (5 mmol) in nitromethane (8 ml). The initially colourless solution is stirred until a yellow colour persists. Aqueous Na₂S₂O₃ (sat. soln. 10 ml) is then added (for basic substrates, Na₂CO₃ is also added to make the mixture alkaline). The mixture is extracted with CH₂Cl₂ (2 × 25 ml) and the dried (Na₂SO₄) extracts are evaporated to yield the sulfoxides.

The silver oxide oxidation of aldehydes to carboxylic acids is aided by the addition of benzyltriethylammonium chloride; the active agent is thought to be TEBA-Ag(OH) [16].

The one-pot conversion of nitroalkyl derivatives into vinyl nitriles under basic conditions in the presence of carbon disulphide and tetra-*n*-butylammonium bromide involves two steps. The initial reduction of the nitro group to the oxime is more effective under solid:liquid phase-transfer conditions (see Chapter 11.8), whereas the second step is conducted under liquid:liquid two-phase conditions [17]; the intermediate oxime is not isolated. Nitriles have also been produced under analogous reaction conditions in good yields starting from the oximes [18, 19]. The mechanism of the dehydration is considered to be analogous to the Chugaev reaction and the isolation of methyl xanthates from reactions to which iodomethane is added supports this hypothesis [18].

10.8.8 Conversion of oximes into nitriles (Table 10.37)

Aqueous NaOH (15%, 1 ml) is added dropwise to the oxime (1.0 mmol) and TBA-HSO₄ (0.5 g, 0.15 mmol) and CS₂ (0.4 ml, 6.6 mmol) in PhH (2 ml). The mixture is stirred for 30 min and the two phases are then separated. The aqueous phase is extracted with PhH (2 × 10 ml) and the combined PhH solutions are dried (Na₂SO₄) and evaporated to yield the nitrile.

10.8.9 Conversion of nitroalkyl compounds into vinyl nitrile derivatives

Step 1: The nitro compound (10 mmol), TBA-Br (0.32 g, 1 mmol), anhydrous K₂CO₃ (0.09 g, 5 mmol), and H₂O (36 µl, 2 mmol) are stirred for 15 min at room temperature.

TABLE 10.37
Selected examples of nitriles from oximes

RCH=NOH	Reaction conditions	% yield
R= Ph	10.8.8 /19 h	80
4-MeOC ₆ H ₄	10.8.8 /30 min	90
4-HOC ₆ H ₄	10.8.8 /1.5 h	80
4-ClC ₆ H ₄	10.8.8 /30 min	85
4-O ₂ NC ₆ H ₄	10.8.8 /30 min	78
2-HOC ₆ H ₄	10.8.8 /1.5 h	77
2-ClC ₆ H ₄	10.8.8 /30 min	70
PhCH=CH	10.8.8 /3 h	86
<i>n</i> -C ₆ H ₁₃	10.8.8 /5 h	64
Me ₂ C=CH(CH ₃) ₂ CHMeCH ₂	10.8.8 /20 h	83

TABLE 10.38
Selected examples of nitriles from nitroallyl compounds

RCH ₂ NO ₂	Reaction time step 1	Reaction time step 2	% yield
R= cyclohex-1-en-1-yl	8 h	2 h	37
4-Methylcyclohex-1-en-1-yl	8 h	2 h	54
6-Methylcyclohex-1-en-1-yl	5 h	3 h	55
4- <i>t</i> -Butylcyclohex-1-en-1-yl	14 h	4 h	60
6-Phenylcyclohex-1-en-1-yl	25 h	2 h	60
cyclohept-1-en-1-yl	24 h	2 h	60
cyclooct-1-en-1-yl	168 h	3 h	64
cyclodec-1-en-1-yl	66 h	2 h	72
3,4-Dihydronaphth-1-yl	8 h	2 h	63
6-Phenylfulven-6-yl	72 h	24 h	56

CS₂ (0.9 ml, 15 mol) is added and the mixture is stirred for a further period (Table 10.38). *Step 2*: CS₂ (4 ml, 67 mmol) is added, followed by the dropwise addition of aqueous NaOH (15%, 10 ml) over a period of 90 min. The mixture is stirred (Table 10.38) and the organic phase is then separated, washed with HCl (10%), aqueous NaHCO₃ (5%) and H₂O, dried (MgSO₄), and evaporated to yield the nitrile.

Several examples have been reported of the use of palladium-mediated oxidation reactions of alcohols and alkyl halides. Palladium(II) acetate in the presence of iodobenzene converts primary and secondary alcohols into carbonyl compounds under solid-liquid two-phase conditions [20]. However, other than there being no further oxidation to carboxylic acids, the procedure has little to commend it over other methods. It is relatively slow with reaction times in the order of 2 days needed to achieve yields of 55–100%.

10.8.10 Palladium-catalysed oxidation of alcohols

The alcohol (2–8 mmol) is added to $\text{Pd}(\text{OAc})_2$ (10 mg, 0.045 mmol), TBA-Cl (0.47 g, 1.68 mmol), NaHCO_3 (0.59 g, 7 mmol) and PhI (2–8 mmol) and the mixture is stirred for 48 h at room temperature under N_2 . When the alcohol has been consumed, as shown by GLC analysis, H_2O (50 ml) is added to the mixture and the aqueous mixture is extracted with Et_2O (3×25 ml). The extracts are washed with H_2O (2×25 ml), dried (Na_2SO_4), and evaporated to yield the carbonyl compound [e.g. EtCHO , 97%; $n\text{-PrCHO}$, 80%; $\text{Me}_2\text{CH}_2\text{CHO}$, 55%; $n\text{-C}_6\text{H}_{13}\text{CHO}$, 75%; PhCHO , 95%; MeCOEt , 100%; $n\text{-C}_6\text{H}_{13}\text{COMe}$, 90%; cyclohexanone, 95%].

$(\text{Ph}_3\text{P})_4\text{Pd}(0)$ and quaternary ammonium salts catalyse the oxidation of benzylic halides by nitrous oxide in a basic medium into *O*-benzylic ethers of the corresponding aryl aldoximes, $\text{ArCH}=\text{NOCH}_2\text{Ar}$ (20–40%) [21]. The procedure does not have a great synthetic appeal.

A more valuable metal-catalysed reaction is the specific dehydrogenation of secondary benzylic alcohols to produce ketones. Chlorodicarbonylrhodium(I) dimer catalyses the dehydrogenation of the alcohols under basic conditions in the presence of phase-transfer catalysts [22]. There is strong evidence of the intermediate formation of an *ortho*-bonded aryl-rhodium complex, which directs the hydrogen abstraction to the benzylic position. Hydroxyl groups at other positions are not affected. The hydrogen transfer does not involve the liberation of hydrogen and reactions conducted under an atmosphere of carbon monoxide inhibits the dehydrogenation, presumably by the formation of an 18-electron ligand carbon monoxide complex, which prevents the *ortho*-metallation.

10.8.11 Specific dehydrogenation of secondary benzylic alcohols (Table 10.39)

The alcohol (5 mmol) and $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (78 mg, 0.2 mmol) in PhH (25 ml) are stirred under N_2 at room temperature with Aliquat or TEBA-Cl (2 mmol) in aqueous NaOH (8M, 20 ml) for 18–30 h (or 4 h at 55 °C). The organic phase is separated, dried (Na_2SO_4), and evaporated to yield the aryl ketones.

TABLE 10.39

Rhodium-catalysed dehydrogenation of benzyl alcohols

Alcohol	Product	% yield
4-MeC ₆ H ₄ CH(OH)Ph	4-MeC ₆ H ₄ COPh	62
PhCH(OH)Me	PhCOMe	78
4-MeOC ₆ H ₄ CH(OH)Me	4-MeOC ₆ H ₄ COMe	57
PhCH(OH)(CH ₂) ₂ OH	PhCO(CH ₂) ₂ OH	46
Dibenzosuberol	Dibenzosuberone	64
1-Ferrocenylethanol	Acetylferrocene	81
2-NaphthylCH ₂ OH	2-Naphthaldehyde	42

Primary benzylic alcohols are oxidized by carbon tetrachloride and ruthenium(III) salts under basic conditions to the corresponding benzaldehydes (>90%) in the presence of didecyldimethylammonium bromide [23]. The reaction has general application, although ring-halogenated systems undergo hydrogenolytic cleavage of the halogen.

10.8.12 Oxidation of primary benzylic alcohols

The alcohol (0.1 mol), Na_2CO_3 (0.1 mol), hydrated RuCl_3 (0.21 g, 1 mmol) and DDDMA-Br (0.81 g, 2 mmol) in CCl_4 (34 ml) are refluxed for 3 h. The mixture is filtered and the solvent evaporated to yield the benzaldehyde.

The epoxidation of alkenes using iodosylbenzene, with tetra-*n*-butylammonium bromide and a manganese or cobalt polytungstate as co-catalysts [24], appears to have little advantage as a synthetic procedure over other methods. *n*-Hexene produces the oxirane (58%), when catalysed by the manganese salt, whereas norbornene is more readily converted (96%) into the oxirane with the cobalt salt.

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Reduction of Organic Compounds

11.1 INTRODUCTION

Compared with other phase-transfer catalysed reactions, reduction of organic compounds has received little attention. This results, to a large extent, from the nature of the available anionic reducing agents. For example, lithium aluminium hydride is too reactive for it to be used in conjunction with an aqueous phase and, although several quaternary ammonium aluminium hydrides have been prepared by metathesis from lithium aluminium hydride [e.g. 1–3], there appears to be relatively few records of their use in phase-transfer catalysed reactions [e.g. 4], and the stoichiometric use of the preformed quaternary ammonium salt has relatively little advantage over the direct use of lithium aluminium hydride. In contrast, although the less active borohydride anion can be transferred effectively from aqueous solutions into organic solvents, its reducing power is lessened in the organic phase, as shown by the recrystallization of the tetra-*n*-butylammonium salt from acetone [5, 6]. It is the selectivity of the quaternary ammonium borohydrides to reduce aldehydes in the presence of other reducible groups, together with its conversion into diborane in non-ethereal solvents, which gives some value to the preparation of the quaternary ammonium hydrido salts. Although the rate of the hydride reductions is enhanced by quaternary ammonium salts, they are generally used at a stoichiometric level and the attractiveness of the phase-transfer catalysis is lost. Hydridometal carbonyl reductions and reductions using dithionite are catalysed by quaternary ammonium salts, as are catalytic hydrogenation reactions.

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11.2 THE USE OF QUATERNARY AMMONIUM ALUMINIUM HYDRIDES

Solid lithium aluminium hydride can be solublized in non-polar organic solvents with benzyltriethylammonium chloride. Initially, the catalytic effect of the lithium cation in the reduction of carbonyl compounds was emphasized [1–3], but this has since been refuted. A more recent evaluation of the use of quaternary ammonium aluminium hydrides shows that the purity of the lithium aluminium hydride and the dryness of the solvent are critical, but it has also been noted that trace amounts of water in the solid:liquid system are beneficial to the reaction [4]. The quaternary ammonium aluminium hydrides have greater hydrolytic stability than the lithium salt; the tetramethylammonium aluminium hydride is hydrolysed slowly in dilute aqueous acid and more lipophilic ammonium salts are more stable [4, 5].

In general, the rates of reduction by the ammonium salts are slower than those attained under normal conditions with the lithium salts, but the use of a non-ethereal solvent can be an advantage. Quaternary ammonium aluminium hydrides reduce ketones and amides effectively to alcohols and amines. Nitriles are also reduced to amines, whereas haloalkanes and arenes are reductively dehalogenated to give hydrocarbons in high yield [3].

11.2.1 Quaternary ammonium aluminium hydrides [4–9]

Method A: LiAlH_4 in THF (0.233 M, 240 ml) is added to a suspension of TMA-SPh (8.98 g) in THF (110 ml), obtained from TMA-OH (4.56 g, 50 mmol) and PhSH (5.5 g, 50 mmol). The mixture is stirred for 2 days at 63°C. The suspended solid is collected, washed well with THF, dried at room temperature under reduced pressure to yield TMA- AlH_4 .

Method B: THA-Br (5.43 g, 12.5 mmol) and an excess of LiAlH_4 are stirred in PhMe (50 ml) for 3 days. The mixture is centrifuged and the supernatant solution containing THA- BH_4 (with some residual THA-Br) is decanted and evaporated.

Method C: TBA-Br (10.8 g, 33.5 mmol) and NaAlH_4 (2.2 g, 41 mmol) are added to THF (200 ml) and the mixture is stirred for 1 h until all of the material has dissolved. Et_2O (400 ml) is added to precipitate the product, which is collected, washed with Et_2O (200 ml), and dried at 80°C for 1 h to give TBA- AlH_4 with 96% purity.

TABLE 11.1

Solid:liquid phase-transfer catalysed reduction using lithium aluminium hydride

Substrate	Product	Reaction conditions	% yield
cyclohexanone	cyclo- $\text{C}_6\text{H}_{11}\text{OH}$	TEBA-Cl/80°C/6 h (PhH) THA-Br/25°C/0.5 h (PhH)	>96 100
MeCONEt_2	Et_3N	TEBA-Cl/80°C/6 h (xylene)	86
PhCN	PhCH_2NH_2	TEBA-Cl/80°C/1 h (PhH)	86
PhBr	PhH	TEBA-Cl/80°C/6 h (PhMe)	62
$n\text{-C}_6\text{H}_{13}\text{Br}$	$n\text{-C}_6\text{H}_{14}$	TEBA-Cl/80°C/6 h (PhH)	92

11.2.2 General reduction procedure using quaternary ammonium aluminium hydrides

The quaternary ammonium salt (0.1 mmol) is added with stirring to LiAlH_4 (38 mg, 1 mmol) in PhMe (10 ml) under N_2 . The substrate (2 mmol) is added and the mixture heated (Table 11.1). Excess hydride is destroyed by the cautious addition of aqueous NH_4Cl (10%) and the organic phase is separated, dried (MgSO_4), and evaporated to give the reduced product.

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11.3 THE USE OF QUATERNARY AMMONIUM BOROHYDRIDES

For many years, prior to the development of current phase-transfer catalytic techniques, tetraalkylammonium borohydrides have been used in non-hydroxylic solvents [see, e.g. 1, 2]. Originally, the quaternary ammonium borohydrides were obtained by metathesis in water or an alcohol [3, 4]. However, with greater knowledge of the phase-transfer phenomenon, an improved procedure has been developed in which the ammonium salt is transferred into, and subsequently isolated from, dichloromethane [5, 6]. In principle, it should be possible to transfer the quaternary ammonium borohydride for use in any non-miscible organic solvent. It should be noted, however, that quaternary ammonium cations are susceptible to hydrogenolysis by sodium borohydride in dipolar aprotic solvents to yield tertiary amines [4].

Early use of the low-molecular-weight quaternary ammonium borohydrides in hydrocarbon solvents showed little advantage over the use of sodium borohydride in aqueous or alcoholic media. Although the ammonium salts in benzene appeared to be capable of effecting all the normal reductions exhibited by the sodium salt in water, they appeared to be generally less reactive. This is well illustrated by the recrystallization of tetra-*n*-butylammonium borohydride from acetone, if the operation is performed rapidly [5, 6].

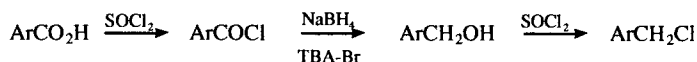
Although there is evidence that quaternary ammonium salts are cleaved by sodium borohydride at high temperature [7], initial studies suggested that the quaternary ammonium borohydrides might have some synthetic value in their selectivity, e.g. aldehydes are reduced by an excess of the quaternary ammonium salts under homogeneous conditions in benzene at 25°C, whereas ketones are recovered unchanged and are only partially reduced at 65°C [2]. The reduction of esters also requires the elevated temperature, whereas nitriles are not reduced even after prolonged reaction at 65°C. Evidence that the two-phase (benzene:water) reduction of octan-2-one by sodium borohydride was some 20–30 times faster in the presence of Aliquat, than in the absence of the catalyst [8], established the potential use of the more lipophilic catalysts.

Kinetic studies established that tetra-*n*-butylammonium borohydride in dichloromethane was a very effective reducing agent and that, by using stoichiometric amounts of the ammonium salt under homogeneous conditions, the relative ease of reduction of various classes of carbonyl compounds was the same as that recorded for the sodium salt in a hydroxylic solvent, i.e. acid chlorides >> aldehydes > ketones >> esters. However, the reactivities, ranging from rapid reduction of acid chlorides at –78°C to incomplete reduction of esters at four days at 25°C, indicated the greater selectivity of the ammonium salts, compared with sodium borohydride [9], particularly as, under these conditions, conjugated C=C double bonds are not reduced.

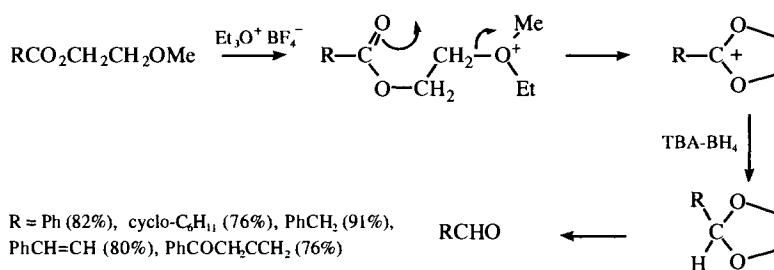
The facile homogeneous catalysed reduction of acid chlorides to alcohols has many advantages over reduction with sodium borohydride in hydroxylic solvents where rapid reaction of the acid chloride with the solvent can occur [10]. The procedure has been incorporated into a simple one-pot conversion of aryl chlorides into the corresponding benzyl chlorides (Scheme 11.1) under liquid:liquid or solid-liquid two-phase conditions [11]. The reduction of a limited number of aryl compounds was reported with *ca.* 70% overall yields, although poorer yields result from the reduction of 4-nitro-, 2-cyano- and 2,4-dichlorobenzoyl chlorides, and the reduction failed completely with terphthaloyl chloride and with its 2,3,5,6-tetrafluoro derivative [11].

Although it has been found possible to isolate the intermediate aldehyde in the reduction of the acid chlorides using sodium borohydride in the presence of dimethylformamide, no analogous procedure has been developed for use under phase-transfer conditions [12].

Using essentially the same reduction technique, 2-methoxyethyl esters have been converted into aldehydes [13] via the dioxalonium cations (Scheme 11.2) in a manner superior to earlier recorded procedures. Although there is a potential for diborane to be formed in the last step, no subsequent reactions involving this species have been observed.



Scheme 11.1



Scheme 11.2

11.3.1 Preparation of tetra-*n*-butylammonium borohydride

Aqueous NaOH (5M 250 ml) is added to TBA-HSO₄ (339 g, 1.0 mol) in H₂O (200 ml). NaBH₄ (41.6 g, 1.1 mol) in H₂O (100 ml) is then added at room temperature and the aqueous mixture is stirred with CH₂Cl₂ (500 ml). The two phases are separated and the aqueous phase is extracted with CH₂Cl₂ (250 ml). The combined CH₂Cl₂ solutions are dried (K₂CO₃) and evaporated under reduced pressure to give a quantitative yield of TBA-BH₄, which can be recrystallized from EtOAc.

11.3.2 Reduction of carbonyl groups using tetra-*n*-butylammonium borohydride

Method A: The carbonyl compound (10 mmol) is added to TBA-BH₄ (2.57 g, 10 mmol) in CH₂Cl₂ (10 ml) at room temperature. The mixture is allowed to stand at room temperature (Table 11.2). Aqueous H₂O₂ (35%, 20 ml) and aqueous NaOH (10%, 10 ml) are then

TABLE 11.2

Stoichiometric reduction of carbonyl compounds with tetraalkylammonium borohydrides

Substrate	Reaction conditions	Product	% yield
PhCOCl	11.3.2.A/15 min ^a	PhCH ₂ OH	98
PhCHO	11.3.2.A/24 h ^b	PhCH ₂ OH	91 ^c
4-ClC ₆ H ₄ CHO	11.3.2.B/20 h	4-ClC ₆ H ₄ CH ₂ OH	87
4-O ₂ NC ₆ H ₄ CHO	11.3.2.B/20 h	4-O ₂ NC ₆ H ₄ CH ₂ OH	88
4-MeOC ₆ H ₄ CHO	11.3.2.B/20 h	4-MeOC ₆ H ₄ CH ₂ OH	53 ^d
2-Furyl-CHO	11.3.2.B/20 h	2-Furyl-CH ₂ OH	83
PhCH=CHCHO	11.3.2.A/17 h ^b	PhCH=CHCH ₂ OH	73
<i>n</i> -C ₈ H ₁₇ CHO	11.3.2.B/20 h	<i>n</i> -C ₉ H ₁₉ OH	75
Citronellal	11.3.2.B/20 h	Citronellol	77
PhCOMe	11.3.2.A/45 h	PhCH(OH)Me	93
<i>n</i> -C ₆ H ₁₃ COMe	11.3.2.B/20 h	<i>n</i> -C ₆ H ₁₃ CH(OH)Me	12 ^e
cyclohexanone	11.3.2.A/24 h	cyclo-C ₆ H ₁₁ OH	86
<i>t</i> -BuCOMe	11.3.2.A/48 h	<i>t</i> -BuCH(OH)Me	82 ^f
<i>n</i> -C ₁₁ H ₂₃ CO ₂ Et	11.3.2.A/96 h	<i>n</i> -C ₁₂ H ₂₅ OH	25 ^g
PhCO(CH ₂) ₂ CO ₂ Me	11.3.2.A/40 h	4-Phenylbutyrolactone	98 ^h
Me ₂ C=CH(CH ₂) ₂ COMe	11.3.2.A/24 h	Me ₂ C=CH(CH ₂) ₂ CH(OH)Me	87

^a at -78°C. ^b Using 2.5 : 1 ratio of substrate:borohydride. ^c 89% by 11.3.2.B after 20 h. ^d 47% recovered aldehyde. ^e 83% recovered ketone. ^f 97% after 5.5 h reflux in CHCl₃. ^g ca. 70% recovered ester. ^h + a trace of PhCH(OH)(CH₂)₂CO₂Me.

added to quench the reduction and the mixture is stirred for 2 h. The aqueous phase is separated and extracted with CH_2Cl_2 (3×30 ml). The combined organic solutions are washed with saturated aqueous Na_2SO_3 (20 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The residue is triturated with Et_2O and the ethereal solution is filtered through alumina and evaporated to yield the reduced product.

Method B: As for 11.3.2.A, except TEBA- BH_4 (2.06 g, 10 mmol) is used.

11.3.3 One-pot conversion of 2-methoxyethyl esters into dioxolanes

The 2-substituted 1,3-dioxalonium salt in CH_2Cl_2 , obtained by refluxing the 2-methoxyethyl ester (10 mmol) and $\text{Et}_3\text{O}^+\text{BF}_4^-$ (4.0 g, 21 mmol) in CH_2Cl_2 (10 ml) for 20 h, is added dropwise with stirring under N_2 to TBA- BH_4 (3.0 g, 12 mmol) in CH_2Cl_2 (20 ml) at -10°C . The reaction mixture is then poured into aqueous NaOH (10%, 50 ml) at 0°C and the organic layer is separated, washed with aqueous NaOH (1M, 2×25 ml), dried (K_2CO_3), and evaporated. The residue is triturated with Et_2O (100 ml) and the filtered ethereal solution is fractionally distilled to give the dioxolane.

11.3.4 One-pot conversion of aromatic acids into benzyl chlorides

SOCl_2 (6.5 g, 55 mmol) is added dropwise with stirring over 15 min to the aromatic acid (50 mmol) and DMF (8 drops) in PhMe (100 ml) at 60°C . The temperature of the mixture is allowed to rise slowly to *ca.* 100°C and the mixture is then refluxed for 2.5 h. After cooling the mixture to *ca.* 15°C , TBA-Br (0.2 g, 0.6 mmol) in H_2O (10 ml) is added. NaBH_4 (2.0 g, 53 mmol) is then added with stirring in five equal portions over 30 min and the mixture is stirred for a further 2 h. The organic phase is separated, dried by azeotropic distillation, and SOCl_2 (6.5 g, 55 mmol) is added dropwise at 90°C . The mixture is maintained at 90 – 100°C for 1 h. Fractional distillation of the mixture gives the benzyl chloride.

Preformed tetra-*n*-butylammonium borohydride used in stoichiometric quantities under homogeneous conditions is considerably more selective for 1,4-reduction of conjugated ketones than are sodium or lithium borohydrides, for example, cyclohex-2-enones are reduced rapidly in toluene to a mixture of the cyclohexanones and cyclohexanols in a combined yield of *ca.* 90%, together with the cyclohex-2-enol (10%) [14]. The dielectric constant of aprotic solvents has little influence on the ratio of 1,2- and 1,4-reduction products, but where the solvent is capable of H-bonding with the carbonyl group the relative amount of the 1,2-reduction product is increased. Selectivity is also lowered when sodium borohydride and a quaternary ammonium salt are used under liquid:liquid or solid:liquid catalytic conditions [14]. Reduction of 2'-hydroxychalcones produces 2,4-*cis*-flavan-4-ols, presumably via an initial base-catalysed ring-closure followed by reduction of the carbonyl group [15].

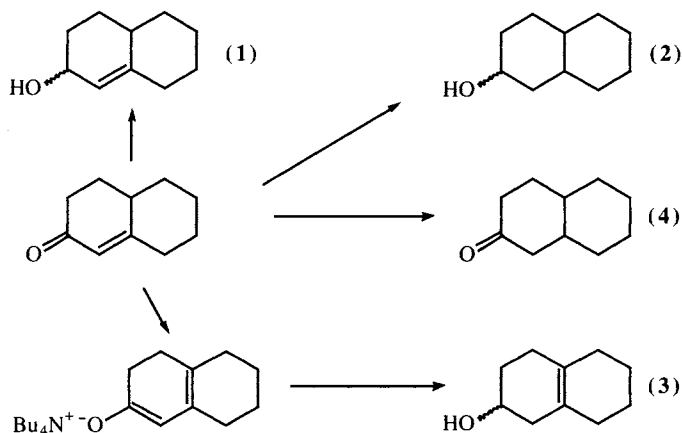
11.3.5 2,4-*cis*-Flavan-4-ols

NaBH_4 (0.38 g) and TBA- HSO_4 (0.5 g, 1.5 mmol) in aqueous NaOH (5M, 15 ml) are stirred with the 2'-hydroxychalcone (1 mmol) in CH_2Cl_2 (30 ml) at room temperature for

6–8 h. The organic phase is then separated, washed with H_2O (3×50 ml), dried (Na_2SO_4), and evaporated to yield the flavanol (80–90%).

Attempts to induce stereochemical control in the reduction of prochiral ketones and imines have been reported using chiral ammonium borohydrides [e.g. 16] (see Chapter 12).

A difference in the reactivities and selectivities between tetra-*n*-butylammonium borohydride and sodium borohydride in the reduction of conjugated ketones is well illustrated with $\Delta^{1,9}$ 2-octalone (Scheme 11.3) [17]. Reduction with the sodium salt in tetrahydrofuran is relatively slow and produces the allylic alcohol (**1**) and the saturated alcohol (**2**) in a 1.2 : 1 ratio whereas, in contrast, tetra-*n*-butylammonium borohydride produces the non-conjugated alcohol (**3**) (50%) and the saturated alcohol (**2**) (47%), with minor amounts of the ketone (**4**), and the allylic alcohol (**1**) [16]. It has been proposed that (**3**) results from an initial unprecedented formation of a dienolate anion and its subsequent reduction.



Scheme 11.3

Much emphasis has been placed on the selectivity of quaternary ammonium borohydrides in their reduction of aldehydes and ketones [18–20]. Predictably, steric factors are important, as are mesomeric electronic effects in the case of 4-substituted benzaldehydes. However, comparison of the relative merits of the use of tetraethylammonium, or tetra-*n*-butylammonium borohydride in dichloromethane, and of sodium borohydride in isopropanol, has shown that, in the competitive reduction of benzaldehyde and acetophenone, each system preferentially reduces the aldehyde and that the ratio of benzyl alcohol to 1-phenylethanol is invariably *ca.* 4 : 1 [18–20]. Thus, the only advantage in the use of the ammonium salts would appear to facilitate the use of non-hydroxylic solvents. In all reductions, the use of the more lipophilic tetra-*n*-butylammonium salt is to be preferred and the only advantage in using the tetraethylammonium salt is its ready removal from the reaction mixture by dissolution in water.

Although the exact mechanism is speculative, it has been found that carboxylic acids, but not esters, are reduced directly to the corresponding alcohols on reaction with benzyltriethylammonium borohydride in the presence of trichlorosilane [21]. Yields are generally in excess of 85%. The failure of the system to reduce esters suggests that diborane is not produced during the reaction [22].

11.3.6 Direct reduction of carboxylic acids to alcohols

HSiCl_3 (0.54 g, 4 mmol) in CH_2Cl_2 (2 ml) is added to TEBA- BH_4 (0.82 g, 4 mmol) in CH_2Cl_2 (6 ml) at 0°C . The mixture is stirred for *ca.* 10 min and the acid (2 mmol) in CH_2Cl_2 (4 ml) then added. The mixture is stirred at room temperature for 3–6 h until the reduction is complete. Aqueous NaHCO_3 (10%, 15 ml) is added and the mixture is extracted with Et_2O (3×25 ml). The ethereal extracts are washed well with aqueous NaHCO_3 (sat. soln), H_2O and brine, dried (Na_2SO_4), and evaporated to yield the alcohol [e.g. 85% *n*- $\text{C}_6\text{H}_{11}\text{OH}$ (4 h); 96% $\text{HS}(\text{CH}_2)_2\text{OH}$ (6 h); 96% cyclo- $\text{C}_6\text{H}_{11}\text{CH}_2\text{OH}$ (4 h); 92% $\text{MeOCO}(\text{CH}_2)_8\text{OH}$ (2.5 h); 88% $\text{Ph}(\text{CH}_2)_2\text{OH}$ (4 h); 92%, PhCH_2OH (5 h)].

Amides are generally reduced only under forcing conditions [23–25]; their reduction with sodium borohydride normally requires the presence of a co-reagent, which is capable of complexation with the carbonyl group [10, 23]. In contrast, the homogeneous reduction by tetra-*n*-butylammonium borohydride in dichloromethane under stoichiometric conditions is highly effective for the conversion of unhindered benzamides into benzylamines (> 70%) and, to a lesser extent (50–60%) for the analogous conversion of *N,N*-disubstituted benzamides and aliphatic amides (Table 11.3). The selectivity of the procedure is such that it has considerable potential for the reduction of amides in the presence of ester groups [26].

Although the hydride reduction of nitriles frequently requires the use of vigorous conditions (LiAlH_4 , B_2H_6), aryl nitriles and benzyl nitriles are reduced to the

TABLE 11.3
Reduction of amides

Amide	Amine ^a	% yield	% recovered amide
PhCONH_2	PhCH_2NH_2	70	8
PhCONHEt	PhCH_2NHEt	75	7
PhCONEt_2	$\text{PhCH}_2\text{NEt}_2$	51	31
PhCONHPh	PhCH_2NHPh	70	14
PhNHCOMe	PhNHEt	74	1
PhNMeCOMe	PhN(Me)Et	53	15
$\text{Ph}(\text{CH}_2)_2\text{CONH}_2$	$\text{Ph}(\text{CH}_2)_3\text{NH}_2$	55	16
$\text{Ph}(\text{CH}_2)_2\text{NHCOMe}$	$\text{Ph}(\text{CH}_2)_2\text{NHEt}$	58	12
$\text{Ph}(\text{CH}_2)_2\text{N(Et)COMe}$	$\text{Ph}(\text{CH}_2)_2\text{NEt}_2$	50	29
4-MeCONHC ₆ H ₄ CO ₂ Et	4-EtNHC ₆ H ₄ CO ₂ Et	77	0
<i>N</i> -Acetylindoline	<i>N</i> -Ethylindoline	55	33
3,4-Dihydroquinolin-2-one	1,2,3,4-Tetrahydroquinoline	86	0

^a Isolated as hydrochloride salt.

corresponding amines in good yields by tetra-*n*-butylammonium borohydride [26] under conditions analogous to those described for the reduction of amides. The procedure is sufficiently selective to allow the preferential reduction of the nitrile substituents in the presence of nitro and chloro groups.

11.3.7 Reduction of amides and nitriles to amines (Tables 11.3 and 11.4)

TBA-BH₄ (1.97 g, 7.65 mmol) is added to the amide or nitrile (2.55 mmol) in CH₂Cl₂ (15 ml) and the mixture is stirred under reflux for 10 h. The solvent is removed under reduced pressure and the residue is dissolved in aqueous HCl (10%, 15 ml). The acidic mixture is extracted with CH₂Cl₂ (10 ml), and neutralized with solid NaOH and extracted with Et₂O (2 × 20 ml). The dried (MgSO₄) ethereal extracts are evaporated to give the amine, which may be isolated as its hydrochloride salt by the passage of dry HCl through a solution of the amine in CH₂Cl₂.

TABLE 11.4
Reduction of nitriles

Nitrile	Amine ^a	% yield
PhCH ₂ CN	PhCH ₂ CH ₂ NH ₂	72
Ph ₂ CHCN	Ph ₂ CHCH ₂ NH ₂	80
4-ClC ₆ H ₄ CH ₂ CN	4-ClC ₆ H ₄ CH ₂ CH ₂ NH ₂	64
4-O ₂ NC ₆ H ₄ CH ₂ CN	4-O ₂ NC ₆ H ₄ CH ₂ CH ₂ NH ₂	53
PhCN	PhCH ₂ NH ₂	71
4-MeC ₆ H ₄ CN	4-MeC ₆ H ₄ CH ₂ NH ₂	87
α-NaphthylCN	α-NaphthylCH ₂ NH ₂	68

^a Isolated as hydrochloride salt.

Although reductive cleavage of aliphatic carbon-halogen bonds and the carbon sulphur bonds of alkane sulphonic esters generally requires vigorous conditions (e.g. LiAlH₄) [27], hydrogenolysis has been effected with sodium borohydride under anhydrous conditions in dipolar solvents. The procedure has been extended to the use of quaternary ammonium borohydrides under phase-transfer conditions [28]. With an excess of the borohydride, primary bromoalkanes are converted quantitatively into the alkanes at room temperature; chloroalkanes generally require higher temperatures (*ca.* 80°C), whereas fluoro compounds are inert to the reductive conditions. The hydrogenolysis of iodoalkanes, which might be expected to be hampered by the high solubility of the quaternary ammonium iodides in the organic phase, proceeds normally (and exothermically). Secondary haloalkanes require more vigorous conditions and may be used as solvents for hydride reductions.

Vinylid halides are virtually unreactive and a high selectivity is to be found in the preferential cleavage of aliphatic carbon-halogen bonds of haloalkanoic amides and esters, and of nitro- and cyanoaryl derivatives. Activated haloarenes, e.g. 1-chloro-2,4-dinitrobenzene, however, give a complex mixture of products [7].

Trithiocarbonate *S,S*-dioxides are reduced to the trithiocarbonates by tetra-*n*-butylammonium borohydride at *ca.* -25°C [29].

11.3.8 Hydrogenolysis of carbon-halogen and carbon-sulphur bonds

An excess of NaBH_4 (Table 11.5) in H_2O (2.6 ml/g) is added dropwise over 30 min to the haloalkane or the sulphonic ester (0.1 mol) and TOA-Br (0.55 g, 1.0 mmol) in PhMe (1 ml/g). On completion of the reduction (Table 11.5) the organic phase is separated, dried (MgSO_4), and fractionally distilled to give the product.

During the hydrogenolysis of primary haloalkanes, diborane is produced and it provides a viable route for its preparation in non-ethereal solvents (see Section 11.5) [5].

Cyclic enol ethers are reductively cleaved to produce α,ω -diols using a stoichiometric amount of benzyltriethylammonium borohydride and chlorotrimethylsilane [30]; acyclic enol ethers give saturated alcohols.

TABLE 11.5
Selected examples of the hydrogenolysis of haloalkanes and alkane sulphonic esters

Substrate	Mol. equiv. of NaBH_4	Reaction conditions	Product	% yield
PhCHClMe	10	11.3.8 / $80^{\circ}\text{C}/3\text{ h}$	PhEt	95
PhCHBrMe	3	11.3.8 / $18^{\circ}\text{C}/4\text{ h}$	PhEt	95
PhCH=CHBr	10	11.3.8 / $80^{\circ}\text{C}/24\text{ h}$	PhCH=CH_2	7 ^a
$\text{PhCH=CHCH}_2\text{Br}$	3	11.3.8 / 18°C	PhCH=CHMe	80
$n\text{-C}_{16}\text{H}_{33}\text{F}$	3	11.3.8 / $80^{\circ}\text{C}/24\text{ h}$	$n\text{-C}_{16}\text{H}_{34}$	0
$n\text{-C}_{16}\text{H}_{33}\text{Cl}$	10	11.3.8 / $80^{\circ}\text{C}/6\text{ h}$	$n\text{-C}_{16}\text{H}_{34}$	95
$n\text{-C}_{16}\text{H}_{33}\text{Br}$	3	11.3.8 / $18^{\circ}\text{C}/6\text{ h}$	$n\text{-C}_{16}\text{H}_{34}$	95
$n\text{-C}_{16}\text{H}_{33}\text{I}$	5	11.3.8 / $18^{\circ}\text{C}/2\text{ h}$	$n\text{-C}_{16}\text{H}_{34}$	92
$\text{Br(CH}_2\text{)}_{10}\text{Br}$	4	11.3.8 / $10^{\circ}\text{C}/5\text{ h}$	$n\text{-C}_{10}\text{H}_{22}$	98
$\text{Br(CH}_2\text{)}_{10}\text{Br}$	1	11.3.8 / $18^{\circ}\text{C}/4\text{ h}$	$n\text{-C}_{10}\text{H}_{21}\text{Br}$	68 ^b
$\text{Br(CH}_2\text{)}_9\text{CHBrMe}$	3	11.3.8 / $18^{\circ}\text{C}/6\text{ h}$	$\text{C}_9\text{H}_{19}\text{CHBrMe}$	97
$\text{Br(CH}_2\text{)}_{11}\text{OH}$	3	11.3.8 / $18^{\circ}\text{C}/6\text{ h}$	$n\text{-C}_{11}\text{H}_{23}\text{OH}$	92
$\text{Br(CH}_2\text{)}_{10}\text{CO}_2\text{Me}$	3	11.3.8 / $10^{\circ}\text{C}/1\text{ h}$	$n\text{-C}_{10}\text{H}_{21}\text{CO}_2\text{Me}$	100
$\text{Br(CH}_2\text{)}_{10}\text{CONMe}_2$	3	11.3.8 / $10^{\circ}\text{C}/1\text{ h}$	$n\text{-C}_{10}\text{H}_{21}\text{CONMe}_2$	100
cyclo- $\text{C}_6\text{H}_{11}\text{Br}$	10	11.3.8 / $80^{\circ}\text{C}/45\text{ h}$	cyclo- C_6H_{12}	83 ^c
PhCH_2Cl	3	11.3.8 / 40°C	PhMe	96
PhCH_2Br	2	11.3.8 / 18°C	PhMe	100
$4\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{Cl}$	3	11.3.8 / 10°C	$4\text{-MeC}_6\text{H}_4\text{NO}_2$	100
$4\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{Br}$	2	11.3.8 / 18°C	$4\text{-MeC}_6\text{H}_4\text{NO}_2$	100
$4\text{-BrC}_6\text{H}_4\text{CH}_2\text{Br}$	2	11.3.8 / 18°C	$4\text{-MeC}_6\text{H}_4\text{Br}$	100
$4\text{-ClC}_6\text{H}_4\text{CH}_2\text{Br}$	2	11.3.8 / 18°C	$4\text{-MeC}_6\text{H}_4\text{Cl}$	96
$4\text{-FC}_6\text{H}_4\text{CH}_2\text{Br}$	2	11.3.8 / 18°C	$4\text{-MeC}_6\text{H}_4\text{F}$	100
$4\text{-CNC}_6\text{H}_4\text{CH}_2\text{Br}$	2	11.3.8 / 18°C	$4\text{-MeC}_6\text{H}_4\text{CN}$	98
$1,4\text{-C}_6\text{H}_4(\text{CH}_2\text{Br})_2$	4	11.3.8 / 18°C	$1,2\text{-Me}_2\text{C}_6\text{H}_4$	100
$4\text{-MeC}_6\text{H}_4\text{SO}_3\text{C}_{12}\text{H}_{25}$	10	11.3.8 / $40^{\circ}\text{C}/5\text{ h}$	$n\text{-C}_{12}\text{H}_{26}$	95
$n\text{-C}_6\text{H}_{13}\text{CH(Me)OSO}_2\text{Me}$	3	11.3.8 / $80^{\circ}\text{C}/48\text{ h}$	$n\text{-C}_8\text{H}_{18}$	80 ^d
$n\text{-C}_{12}\text{H}_{25}\text{OSO}_2\text{Me}$	3	11.3.8 / $40^{\circ}\text{C}/\text{h}$	$n\text{-C}_{12}\text{H}_{26}$	95

^a + 2% $\text{PhC}\equiv\text{CH}$. ^b + 3% $n\text{-C}_{10}\text{H}_{22}$. ^c + 1% cyclo- C_6H_{10} . ^d + 10% $\text{C}_5\text{H}_{11}\text{CH}=\text{CHMe}$.

11.3.9 Reductive cleavage of enol ethers (Table 11.6)

Me_3SiCl (0.43 g, 4 mmol) is added to the enol ether (4 mmol) and TEBA-BH_4 (0.82 g, 4 mmol) in CH_2Cl_2 (6 ml) at 0°C and the mixture is stirred for 6–10 h in contact with air. Aqueous K_2CO_3 (10%, 3 ml) is then added and the organic phase is separated, washed well with water, dried (MgSO_4), and evaporated to yield the saturated alcohol.

TABLE 11.6
Reductive cleavage of enol ethers

Enol ether	Reaction conditions	Product	% yield
2,3-Dihydrofuran	11.3.9/8 h	$\text{HO}(\text{CH}_2)_4\text{OH}$	73
3,4-Dihydro-2H-pyran	11.3.9/8 h	$\text{HO}(\text{CH}_2)_5\text{OH}$	74
5-Ethyl-3,4-dihydro-2H-pyran	11.3.9/7.5 h	$\text{HO}(\text{CH}_2)_4\text{CHOHC}_2\text{H}_5$	69
5-Hexyl-3,4-dihydro-2H-pyran	11.3.9/7 h	$\text{HO}(\text{CH}_2)_4\text{CHOHC}_6\text{H}_{13}$	72
$n\text{-C}_5\text{H}_{11}\text{CH}=\text{CHOC}_2\text{H}_5$	11.3.9/6 h	$n\text{-C}_7\text{H}_{15}\text{OH}$	80
$n\text{-C}_3\text{H}_7\text{C}(\text{OC}_2\text{H}_5)=\text{CHC}_2\text{H}_5$	11.3.9/3 h	$(n\text{-C}_3\text{H}_7)_2\text{CHOH}$	65

Under mild conditions, sodium borohydride does not reduce nitroarenes to the corresponding anilines, but frequently yields a mixture of products in which the ring is hydrogenated or the nitro group is only partially reduced [31]. A study of the reduction of polynitroarenes using sodium borohydride under phase-transfer conditions indicated that activation of the ring by the nitro groups towards nucleophilic hydride attack leads either to reduction of the ring or displacement of the nitro groups [32]. For example, 2,3,4- and 2,4,5-trinitrotoluene are converted into 2,4-dinitrotoluene, whereas, in contrast, the aromatic ring of 2,4,6-trinitrotoluene is reduced, as a consequence of the initial hydride ion attack at the electrophilic 3-position. Competitive reduction of 2,4,5- and 2,4,6-trinitrotoluene, in which the rate of reduction of the ring is more rapid than the nucleophilic displacement of the nitro group, can be rationalized in terms of the greater degree of resonance interaction of the nitro groups, which stabilizes the Meisenheimer intermediate for the symmetrical 2,4,6-trinitro derivative, compared with the 2,4,5-isomer in which the nitro groups will be twisted out of the plane of the ring. Similar activating effects are probably operating in the reduction of the halonitroarenes leading to the complex mixture of products. These results are clearly similar to those recorded for the analogous reaction of sodium borohydride with nitroarenes under homogeneous conditions [31].

11.3.10 Hydrogenolysis of 2,4,5-trinitrotoluene

NaBH_4 (1.9 g, 50 mmol) and TEHDA-Br (2.27 g, 6 mmol) in H_2O (100 ml) are added with stirring to 2,4,5-trinitrotoluene (3.5 g, 0.015 mol) in CH_2Cl_2 (100 ml) at room temperature under N_2 . The mixture is stirred for 1 h and the organic phase is then separated, washed with HCl (6M, 20 ml) and H_2O (3×20 ml), dried (MgSO_4), and evaporated to give 2,4-dinitrotoluene (60%).

Aryl azides are converted into the corresponding anilines by polymer-supported borohydride [33]. Simple aliphatic azides are not reduced under similar conditions and the reduction of benzyl azides is slow.

11.3.11 Reduction of aryl azides

Amberlite IRA-400 (10 g, in Cl⁻ form) and NaBH₄ (1.89 g, 50 mmol) in H₂O (100 ml) are stirred for 1 h. The resin is collected, washed well with H₂O until the washings are free of borohydride, and dried at 65 °C for 8 h.

The resin (0.5 g, \equiv 1.25 mmol BH₄⁻) is added to the aryl azide (1 mmol) in MeOH (15 ml) and the mixture is refluxed until TLC analysis shows complete conversion to the amine. The mixture is filtered and the resin is washed with MeOH (2 \times 10 ml). The combined methanolic solutions are evaporated to yield the amine [e.g. 94% PhNH₂ (3 h); 96% 4-MeC₆H₄NH₂ (18 h); 97% 4-ClC₆H₄NH₂ (4 h); 97% 4-O₂NC₆H₄NH₂ (30 min); 94% PhSO₂NH₂ (6 h); 46% PhCH₂NH₂ (24 h)].

Although hydrogenolysis of chlorobenzenes is not a viable proposition, the reductive cleavage of the carbon–chlorine bond of 5-chloroisoxazoles can be effected in high yield (>70%) under homogeneous conditions using tetra-*n*-butylammonium borohydride [34] (Table 11.7). The procedure is superior to the more usual base-catalysed elimination of a tosylhydrazino group, which is obtained by nucleophilic displacement of the chloro substituent. Ester groups tend to be reduced preferentially, for example, the 5-chloro-3-hydroxymethylisoxazole (80%) is isolated from the reduction of the 5-chloro-3-carboxylic ester. In contrast, in the absence of a phase-transfer catalyst, the carbon–chlorine bond is cleaved preferentially by sodium borohydride in dimethylsulphoxide with little or no concomitant reduction of ester or nitrile groups [34].

TABLE 11.7
Reductive dehalogenation of 3,4-disubstituted 5-chloroisoxazoles

3-substituent	4-substituent	Reaction conditions	% yield
Me	Me	11.3.12/40 °C/24h	50
Me	Ph	11.3.12/20 °C/20h	83
Ph	Me	11.3.12/30 °C/144h	86
Ph	H	11.3.12/20 °C/72h	70
Me	4-BrC ₆ H ₄	11.3.12/20 °C/4h	60
Me	CH ₂ CO ₂ Et	11.3.12/20 °C/240h	15 ^a

^a With 33% 5-chloro-4-(2-hydroxyethyl)-3-methylisoxazole and 12% 4-(2-hydroxyethyl)-3-methylisoxazole.

11.3.12 Reductive cleavage of the carbon–chlorine bond of chloroisoxazoles

TBA-BH₄ (10.27 g, 40 mmol) in CH₂Cl₂ (30 ml) is added to the 5-chloroisoxazole (20 mmol) and the mixture is stirred under N₂ (Table 11.7). The solvent is then removed

under reduced pressure and H_2O (110 ml) and conc. HCl (5 ml) are added to the residue under cooling. The aqueous solution is neutralized with solid NaHCO_3 (ca. 5.2 g), and extracted with Et_2O (3×20 ml). The ethereal extracts are dried (MgSO_4) and evaporated. The residue is triturated with cyclo- C_6H_{12} and the filtered organic solution is evaporated to give the isoxazole.

Alkali metal borohydrides are frequently used for the reduction of π -electron-deficient heteroaromatic systems, but reduction of π -electron-excessive arenes is generally possible only after protonation of the systems [e.g. 35–37]. The use of tetra-*n*-butylammonium borohydride under neutral conditions for the conversion of alkylindoles into indolines [38] is therefore somewhat unusual. Reduction of indoles by diborane under strongly alkaline conditions involves the initial interaction of the indolyl anion with the diborane to form an ‘amino-borane’ which, under the basic conditions, reacts with a second molecule of diborane to produce the indoline [39]. The reaction of tetra-*n*-butylammonium borohydride with indoles could also proceed via the intermediate formation of diborane.

11.3.13 Borohydride reduction of alkylindoles

TBA- BH_4 (2.32 g, 9.0 mmol) is added to the indole (3.0 mmol) in CH_2Cl_2 (20 ml) and the mixture is stirred under reflux for 10 h. The solvent is then removed under reduced pressure and HCl (10%, 15 ml) is added. The aqueous solution is stirred for 30 min at room temperature and then washed with Et_2O (2×20 ml). The acidic solution is neutralized with solid NaOH and extracted with Et_2O (3×15 ml). The dried (MgSO_4) extracts are evaporated to give the indoline (40–70%).

Nucleophilic displacement of alkanesulphonyloxy groups by the hydride ion has been conducted with some success for the conversion of, for example, *O*-trifluoromethylsulphonyl sugars into the corresponding deoxy derivatives [40]. Acetoxy groups prove to be unstable under the reaction conditions, but benzyloxy groups are retained. In some instances, concomitant ring contraction occurs during the reaction. Halo sugars are also converted into deoxy sugars.

Demercuration of organomercury compounds is a critical step in synthetic procedures, which involve mercuriation-initiated cyclization reactions [e.g. 41]. Many of the standard procedures for demercuration result in rearrangement or ring cleavage of the system, but reductive carbon–mercury cleavage (e.g. Scheme 11.4) with an excess of the quaternary ammonium borohydride is effective under phase-transfer conditions [e.g. 42, 43].

11.3.14 Reductive cleavage of carbon–mercury bonds

The organomercury(II) compound (2.0 mmol) in CH_2Cl_2 (5 ml) is added with stirring at room temperature to TEBA- Cl (1.6 g, 7 mmol) in aqueous NaOH (10%, 10 ml). NaBH_4 (0.057 g, 1.5 mmol) in aqueous NaOH (10%, 3 ml) is added and the mixture is stirred for ca. 15 min. The aqueous layer is separated and extracted with CH_2Cl_2 (2×20 ml). The combined organic solutions are dried (MgSO_4) and fractionally distilled under reduced pressure to yield the product.



The relative catalytic activity of 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane borohydride vs tetra-*n*-butylammonium borohydride for range of reductive processes has been examined [45]. It is claimed that the rigid and bulky structure of bicyclic catalyst make it more selective in its catalytic effect. Certainly, it reduces 1-phenyl-2-acetyloxirane cleanly to the corresponding alcohol in 90% yield without cleavage of the ring, whereas the tetra-*n*-butylammonium salt gives a mixture of products under similar conditions. The bicyclic catalyst also appears to be superior for the reduction of acid chlorides; by varying the amount of catalyst it is possible to obtain either the aldehyde or the alcohol. However, close analysis shows that, for many reactions, the yields and ease of reductions with the two catalysts are comparable.

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11.4 'MODIFIED' QUATERNARY AMMONIUM BOROHYDRIDES

Tetra-*n*-butylammonium triborono-octahydride, which can be obtained by metathesis from the sodium salt and tetra-*n*-butylammonium iodide, is a mild reducing agent with a selectivity similar to that of the tetrahydride, but with a much lower overall activity [1]. For example, acid chlorides are reduced five-times more readily than are aldehydes, which are ten-times more susceptible to reduction than acyclic

ketones and twice as reactive as the cyclic ketones. Although the $B_3H_8^-$ anion is capable of transferring eight hydrogen atoms, a threefold excess of the reagent is required to effect the reduction of aldehydes and ketones. The reduction can be made more efficient, however, by the addition of a transition metal ion. The mode of action is not clear, but the addition of manganese chloride, for example, promotes the reduction of 7.8 moles of cyclohexanone by one mole of the triborono-octahydride salt [2].

Quaternary ammonium borohydrides react with diborane to produce the corresponding ammonium diboronoheptahydrides, which behave both as borohydrides and as diborane [3].

11.4.1 Preparation of tetra-*n*-butylammonium triborono-octahydride

The whole of this preparation should be conducted in a sealed system purged with N_2 and with an exit bubbler leading into aniline to remove any volatile boranes, which may be carried over with the gas flow.

I_2 (20.6 g, 81 mmol) in dry diglyme (115 ml) is added dropwise with stirring over 60–90 min to $NaBH_4$ (17 g, 0.45 mol) in anhydrous diglyme (250 ml) under N_2 at 98–102°C. [CAUTION: HYDROGEN will be released as the reaction proceeds.] After the addition of the I_2 , the mixture is heated for a further 2 h at 95°C and then reduced in volume by the passage of dry N_2 through the hot mixture. Aqueous TBA-I (sat. soln, 1000 ml) is added with stirring to the cooled mixture and the precipitated TBA- B_3H_8 (13.4 g, 58%) is collected and is purified by dissolution in CH_2Cl_2 and re-precipitation with Et_2O .

11.4.2 Reductions using tetra-*n*-butylammonium triborono-octahydride

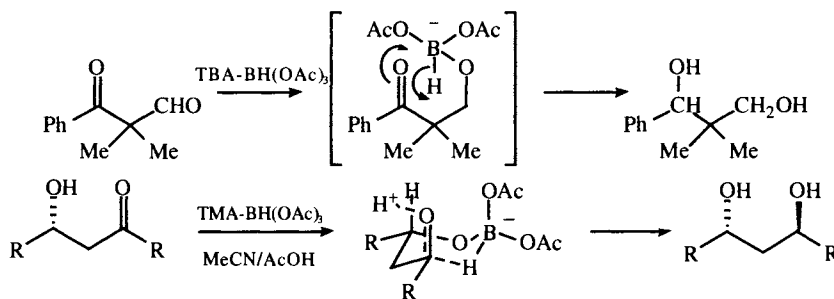
The carbonyl compound (2.16 mmol) is added under N_2 to TBA- B_3H_8 (0.178 g, 0.63 mmol) in $CHCl_3$ (10 ml). The solution is stirred under reflux for 20 h, then washed with HCl (10%, 25 ml) and aqueous $NaHCO_3$ (sat. soln, 2 × 15 ml), dried ($MgSO_4$), and evaporated to yield the alcohol.

11.4.3 Manganese chloride-promoted borohydride reductions

Procedure 11.4.2 is followed, using THF in place of $CHCl_3$, and $MnCl_2 \cdot 2H_2O$ (0.424 g, 0.72 mol) is added gradually over 10 min while the mixture is stirred at room temperature. The alcohol is isolated from the mixture by extraction with Et_2O (2 × 20 ml) and the extracts are washed with acid and $NaHCO_3$, as described in 11.4.2 [e.g. 43% $n-C_6H_{13}CH_2OH$; 99.4% $n-C_6H_{13}CH(OH)Me$; 83% cyclo- $C_6H_{11}OH$; 87.6% $PhCH_2OH$ from $PhCHO$, 65.4% from $PhCOCl$; 99.6% $PhCH(OH)Me$; 60.6% $n-C_7H_{15}OH$ from $n-C_6H_{13}COCl$].

Tetra-*n*-butylammonium trisacetoxyborohydride has been prepared *in situ* in dichloromethane from the borohydride and acetic acid [4,5]. The effectiveness of the reagent for the reduction of aldehydes in the presence of ketones is greater than originally reported using sodium trisacetoxyborohydride [5]. In a series of competitive reductions, aldehydes were reduced to the alcohols (>90%), whereas the ketones

were recovered unchanged (>95%) after 24 hours at 80°C [4]. Similarly, 4-benzoylbenzaldehyde was converted into 4-benzoylbenzyl alcohol (88%), whereas a mixture of the primary and secondary alcohols was obtained, when tetra-*n*-butylammonium borohydride was used under identical conditions; an excess of the borohydride produces the diol (65%). The trisacetoxyborohydride also reduces 4-acetylbenzaldehyde to 4-acetylbenzyl alcohol (72%) and aliphatic keto aldehydes are generally reduced to the corresponding keto alcohols in high yield. However, as noted in the reduction of β -hydroxyketones [6], when the carbonyl groups are separated by only one carbon atom, intramolecular transfer of the hydride ion from the complex promotes reduction of both the keto and aldehyde groups (Scheme 11.5). Reduction of the intermediate hydroxy ketone is stereoselective; the greater stability of the pseudo-axial configuration of the carbonyl group in the transition state leads to the major formation of 'anti' dihydroxy compounds (Scheme 11.5) [7].



Scheme 11.5

α -Hydroxy oximes are stereoselectively reduced by tetramethylammonium trisacetoxyborohydride to yield *syn*-1,2-amino alcohols [8]. Similarly, the reduction of β -hydroxy oximes is stereospecific; *Z*-oximes yield mainly 1,3-*anti*-amino alcohols, whereas the *E*-oximes produce the 1,3-*syn*-isomers in high yield (>85%) [9].

11.4.4 Reduction with tetra-*n*-butylammonium trisacetoxyborohydride

$\text{CH}_3\text{CO}_2\text{H}$ (1.70 ml, 30 mmol) in PhH (10 ml) is added dropwise with stirring to TBA-BH_4 (2.56 g, 10 mmol) in PhH (50 ml) and CH_2Cl_2 (5 ml) at 20°C under N_2 . The solution is stirred at 20°C for 1 h and then heated to 75–80°C. The carbonyl compound (or oxime) (2 mmol) in PhH (10 ml) is added and the mixture is heated under reflux for 24 h. The cooled mixture is poured into H_2O , basified with aqueous NaOH (5M), and extracted with Et_2O . The organic extracts are washed with H_2O (2 \times 20 ml), dried (Na_2SO_4), and evaporated under reduced pressure to give the reduced product. MeCN is used as a solvent for the oximes.

Tetra-*n*-butylammonium cyanoborohydride has been prepared by metathesis from the quaternary ammonium hydrogen sulphate and sodium cyanoborohydride. Other tetraalkylammonium cyanoborohydrides have also been synthesized [10].

Reduction of conjugated carbonyl compounds using stoichiometric amounts of the ammonium salt shows little advantage over the sodium salt in acidic methanol [11] with both reagents producing allylic alcohols (58–88% for acyclic compounds and 15–64% for cyclic compounds) by selective 1,2-reduction of the conjugated systems. Aldehydes, ketones and conjugated enones are also reduced by tetra-*n*-butylammonium cyanoborohydride in HMPA [11, 12], whereas haloalkanes and alkanesulphonic esters are cleaved reductively under similar conditions [13].

Quaternary ammonium cyanoborohydrides have been used for the reduction of iminium salts [14] and in the reductive amination of aldehydes and ketones [15].

11.4.5 Synthesis of tetra-*n*-butylammonium cyanoborohydride

Aqueous NaOH (5M, 35 ml) and NaBH₃CN (6.93 g, 0.11 mol) in H₂O (40 ml) are added with stirring to TBA-HSO₄ (33.95 g, 0.1 mol) in H₂O (50 ml) at room temperature. Stirring is continued for a further 15 min and the aqueous mixture is then extracted with CH₂Cl₂ (3 × 50 ml). The extracts are washed with H₂O (2 × 10 ml), dried (K₂CO₃), and evaporated to yield TBA-BH₃CN (78%), m.p. 144–145 °C, which is recrystallized from EtOAc.

11.4.6 1,2-Reduction of conjugated carbonyl compounds

TBA-BH₃CN (0.82 g, 10 mmol) is added with stirring at room temperature to the carbonyl compound (5 mmol) in MeOH (10 ml), containing a trace of methyl orange indicator. Methanolic HCl (2M) is added dropwise to maintain a red colour with the indicator during the reduction and the mixture is stirred until there is no further change in the colour of the indicator (*ca.* 90 min). The solvent is evaporated under reduced pressure and the residue is dissolved in H₂O (8 ml). The aqueous solution is extracted with Et₂O (3 × 25 ml) and the dried (MgSO₄) ethereal extracts are fractionally distilled to give the allylic alcohol.

11.4.7 Reductive amination of aldehydes and ketones

The carbonyl compound (10 mmol), NaBH₃CN (0.44 g, 7 mmol), and Aliquat (2.83 g, 7 mmol) [or preformed TBA-BH₃CN (1.98 g, 7 mmol)] are added with stirring to the secondary amine (60 mmol) in methanolic HCl (2.5 M, 8 ml) and CH₂Cl₂ (21 ml). 4 Å molecular sieves (1 g) are added and the mixture is stirred at room temperature for 48 h. The filtered mixture is then acidified and evaporated. The residue is taken up in H₂O (10 ml) and washed with Et₂O (3 × 20 ml). The aqueous solution is neutralized with aqueous NaHCO₃ (sat. soln), saturated with NaCl, and extracted with Et₂O. Fractionally distillation of the dried (Na₂SO₄) extracts yields the tertiary amine [e.g. *N*-benzylpyrrolidine, 76%; *N*-benzylmorpholine, 41%; *N*-cyclohexylpyrrolidine, 94%; *N*-(α -methylbenzyl)pyrrolidine, 82%].

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11.5 REDUCTIONS USING DIBORANE

In Section 11.3, the facile reductive cleavage of primary haloalkanes was described in which an important aspect of the reaction was the simultaneous formation of diborane. This route to diborane has several advantages in safety and convenience of preparation over conventional procedures in which sodium borohydride is allowed to react with boron trifluoride-diethyl etherate. The most significant advantage is the possibility of producing diborane in a high boiling and/or non-ethereal solvent, which can be used directly in the next step of a reduction sequence [1]. For example, as primary haloalkanes react more readily with the borohydride anion than do the secondary halides, quaternary ammonium borohydrides can be used in dichloromethane for the generation of diborane. Iodomethane, bromoethane, or 1,2-dichloroethane have all been used for the generation of diborane and the choice of the haloalkane will frequently depend on the boiling point of the reduced product in order to facilitate its isolation and purification. It is recommended that the diborane should be used within a few hours of its preparation, when it has an activity comparable with that of conventionally produced ethereal solutions.

Reduction of carboxylic acids and esters, aldehydes, and nitriles, and the hydroboration of alkenes with diborane in non-ethereal solvents is highly effective (Table 11.8), but reduction of nitro groups or cleavage of arena-halogen bonds does not occur [1]. However, in spite of the potential advantages, very little use appears to have been made of the procedure.

It was initially proposed that reduction of ketones by quaternary ammonium borohydrides in dichloromethane (see Section 11.3) might be accounted for by the initial slow formation of diborane. However, the generation of diborane under such conditions is too slow to have any influence on the reduction.

Phase-transfer generated diborane has been used for the hydroboration of alkenes and their conversion into alcohols [1, 2] and the procedure has also been employed for the cleavage of formamido compounds to yield the amines [3]. Cyclododecan-1,3- and 1,4-diones have been obtained in a 3 : 1 ratio and overall yield of 59% via

TABLE 11.8

Reduction and hydroboration reactions using *in situ* generated diborane

Substrate	Haloalkane	Product	% yield
4-O ₂ NC ₆ H ₄ CO ₂ Me	MeI ^a	4-O ₂ NC ₆ H ₄ CH ₂ OH	80
4-PhCH ₂ OC ₆ H ₄ CH ₂ CO ₂ Et	MeI ^a	4-PhCH ₂ OC ₆ H ₄ CH ₂ CH ₂ OH	87
PhCO ₂ H	EtBr ^b	PhCH ₂ OH	98
3-O ₂ NC ₆ H ₄ CO ₂ H	EtBr ^b	3-O ₂ NC ₆ H ₄ CH ₂ OH	90
4-ClC ₆ H ₄ CO ₂ H	EtBr ^b	4-ClC ₆ H ₄ CH ₂ OH	98
PhCN	MeI ^b	PhCH ₂ NH ₂	95
4-MeOC ₆ H ₄ CH ₂ CO ₂ H	Cl(CH ₂) ₂ Cl ^a	4-MeOC ₆ H ₄ CH ₂ CH ₂ OH	90
cyclo-C ₆ H ₁₀	EtBr ^c	cyclo-C ₆ H ₁₁ OH	98
PhOCH ₂ CH=CH ₂	EtBr ^c	PhO(CH ₂) ₃ OH	70 ^d
3-MeO-4-HOC ₆ H ₃ CH ₂ CH=CH ₂	MeI ^b	3-MeO-4-HOC ₆ H ₃ (CH ₂) ₃ OH	96 ^e

^a With 1.5 equiv of QBH₄. ^b With 1 equiv of QBH₄. ^c With 0.5 equiv of QBH₄. ^d + minor amount of PhOCH₂CH(OH)Me. ^e Isolated as the diacetate.

the hydroboration of cyclododec-3-enone and subsequent oxidation [4]; during the initial hydroboration step, the carbonyl group is also reduced producing 1,3- and 1,4-diols, which are subsequently oxidized to yield the diones.

11.5.1 Diborane reductions

TBA-BH₄ (Table 11.8) in CH₂Cl₂ (400 ml) is azeotropically dried by evaporation of *ca.* 250 ml of the CH₂Cl₂ under reduced pressure. The organic substrate (0.1 mmol) is added under argon and the mixture cooled to 0°C. The haloalkane (0.2 mol) (Table 11.8) is added dropwise and the mixture stirred for 30 min at room temperature. The excess borohydride is destroyed by the addition of EtOH (25 ml) and the solution is neutralized with HCl (20%). The aqueous phase is separated and extracted with CH₂Cl₂ (2 × 20 ml). The combined organic solutions are washed with H₂O (10 ml), dried (MgSO₄), and fractionally distilled to yield the reduced product.

11.5.2 Hydroboration of alkenes

MeI or EtBr (0.15 mol) in CH₂Cl₂ (25 ml) is added with stirring at room temperature to the alkene (0.1 mol) and TBA-BH₄ (Table 11.8) in CH₂Cl₂ (400 ml) and the mixture is refluxed for 30 min. H₂O (10 ml) and aqueous NaOH (2M, 75 ml) are added dropwise to the cooled mixture, followed by the dropwise addition of H₂O₂ (3%, 24 ml). The mixture is stirred for 1.5 h, and the aqueous phase is then separated and extracted with CH₂Cl₂ (2 × 50 ml). The combined organic solutions are dried (Na₂SO₄) and evaporated. The residue is triturated with Et₂O (400 ml) and ethereal solution is evaporated to yield the alcohol.

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11.6 PHASE-TRANSFER CATALYSED REDUCTIONS WITH SODIUM DITHIONITE

Sodium dithionite is well established [1] as a powerful reducing agent under alkaline conditions. Its redox potential is close to that of sodium borohydride [2] and, in several respects, there are advantages in the use of sodium dithionite as an alternative to the metal hydrides under phase-transfer catalytic conditions, particularly in the reduction of carbonyl compounds [3].

The two-phase reduction of cyclohexanones by sodium dithionite in the presence of a stoichiometric amount of Adogen gave higher yields of the cyclohexanols than those obtained by the standard procedure using sodium dithionite in a water:dioxane system (Table 11.9). A marked improvement in yield was also observed with the reduction of sterically hindered 2,6-dimethylcyclohexanone and there was a greater degree of stereoselectivity, which was comparable to that noted for the corresponding reduction with the borohydride ion [4].

The selective 1,4-reduction of α,β -unsaturated carbonyl compounds is always a challenge, but it has been met successfully by the use of dithionite under phase-transfer conditions. Reduction proceeds in high yield to the total exclusion of saturated or allylic alcohols (Table 11.10) [5, 6]. Exocyclic and endocyclic conjugated C=C double bonds are reduced with equal ease, whereas non-conjugated double bonds remain intact. The predominant reduction pathway for conjugated dienoid

TABLE 11.9

Selected examples of the reduction of methylcyclohexanones with dithionite^a

Cyclohexanone derivative	% yield	<i>cis:trans</i> ratio
2-Methyl	76 ^b	1:2.5
3-Methyl	81 ^c	4:1
4-Methyl	82 ^d	1:3.3
2,4-Dimethyl	70 ^e	1.6:2.1 ^f

^a 1:8:6:8 molar ratio of ketone:Na₂S₂O₄:NaHCO₃:Adogen. ^b 63% with 1:2 *cis:trans* ratio in absence of Adogen. ^c 67% with 3:1 *cis:trans* ratio in absence of Adogen. ^d 68% with 1:2 *cis:trans* ratio in absence of Adogen. ^e 15% in absence of Adogen.

^f *cis,cis:trans,trans:trans,cis* ratio.

TABLE 11.10

Selected examples of the 1,4-reduction of conjugated α,β -unsaturated carbonyl compounds with dithionite

Substrate	Reaction conditions	Product	% yield
Citral	11.6.1/1.5 h	Citronellal	69
Carvone	11.6.1/30 min	Dihydrocarvone	82
Piperitone	11.6.1/2 h	Menthone	32
Pulegone	11.6.1/2.5 h	Menthone	42
Isophorone	11.6.1/2 h	Trimethylcyclohexanone	84

^a + 22% isomenthone. ^b + 32% isomenthone.

TABLE 11.11

Selected examples of the dithionite reduction of alkane-2,4-dienoic esters

$R^6R^5C=C(R^4)C(R^3)=C(R^2)CO_2R^1$						$R^6R^5CHC(R^4)=(R^3)CH(R^2)CO_2R^1$	Reaction conditions	<i>E:Z</i> ratio	% yield
R^1	R^2	R^3	R^4	R^5	R^6				
Et	Me	H	H	H	Me ^a		11.6.2/2 h ^b	100% <i>E</i> -isomer	61
Me	H	Me	H	H	R ^{c, d}		11.6.2/1 h ^e	36:64	73 ^f
Me	H	H	Me	H	Me ^a		11.6.2/2 h ^b	72:28	59
Me	H	H	H	Me	R ^{g, h}		11.6.2/2 h ^b	59:41	43 ⁱ
Et	Me	H	H	Me	R ^j		11.6.2/1 h ^b	50:50	14

^a >97% 2*E*,4*E*-isomer. ^b 50% initial addition of Na₂S₂O₄, 25% after 30 min, and 25% after 60 min. ^c 2*E*,4*E*:2*Z*,4*E*-isomer ratio 59:41. ^d R = 2,6-dimethylhept-5-enyl. ^e 66% initial addition of Na₂S₂O₄ and 34% after 30 min. ^f 19% recovered substrate. ^g R = 4-methylpent-3-enyl. ^h 2*E*,4*E*:2*E*,4*Z* isomer ratio 59:41. ⁱ A similar yield and isomer ratio is obtained when the substrate isomer ratio is 96:4. ^j 2*E*,4*E*:2*E*,4*Z* isomer ratio 62:38.

esters yields the non-conjugated alk-3-enoic esters (Table 11.11) [7]; when a stoichiometric amount of sodium dithionite and the quaternary ammonium salt was used, the *E:Z* ratios remained unchanged, but higher yields were obtained [8] (*cf.* the reduction of the corresponding acids in the absence of a phase-transfer catalyst which produces trace amounts (2–7%) of the alk-4-enoic acids, in addition to the alk-3-enoic acids). In contrast, the palladium-catalysed reduction of hexa-2,4-dienoic esters in the presence of trialkylammonium formates produces the conjugated hex-2-enoic esters [9].

11.6.1 1,4-Reduction of conjugated ketones and aldehydes

Na₂S₂O₄ (1.6 g, 9 mmol) is added with stirring under N₂ to the α,β-unsaturated carbonyl compound (1 mmol), Adogen (0.15 g, 0.3 mmol), and NaHCO₃ (1.5 g, 18 mmol) in PhH (25 ml) and H₂O (25 ml). The mixture is heated at 80°C for 30 min–2.5 h. The organic phase is then separated, washed with H₂O (2 × 10 ml), dried (MgSO₄), filtered through silica, and evaporated to give the saturated carbonyl system.

11.6.2 Conversion of alk-2,4-dienoic esters into alk-3-enoates

Na₂S₂O₄ (1.3 g, 7.5 mmol) is added under N₂ to the ester (5 mmol), NaHCO₃ (0.84 g, 10 mmol) and Adogen (0.75 g, 1.5 mmol) in PhH (5 ml) and H₂O (5 ml) and the mixture is stirred at 80°C for 2 h. The aqueous phase is separated and extracted with *n*-C₆H₁₄ (2 × 25 ml). The combined organic solutions are dried (MgSO₄) and evaporated under reduced pressure to give the reduced ester, which is purified by chromatography on silica [An increased yield may be obtained with Adogen (7.5 mmol) and NaHCO₃ (20 mmol)].

The reduction of quinones by sodium dithionite is well established [1] and can be used as a diagnostic test for the presence of the quinonoid system. However, when the procedure is applied to a synthetic sequence, subsequent protection of the newly formed hydroxyl groups is invariably necessary in order to prevent re-oxidation of

the system. Using a phase-transfer catalyst, the reduction and subsequent *O*-alkylation is now a simple technique and it can be effected as a 'one-pot' process [10]. Additionally, the higher benzo analogues of 1,4-benzoquinones can be reduced easily and, with the exception of amino derivatives, quinones bearing electron-donating substituents can be readily converted into the dimethoxyarenes. Halogen substituents attached to the aromatic systems are retained during the reduction (see Table 11.12) [11].

TABLE 11.12
One-pot reductive methylation of quinones

Quinone	Product	% yield
1-Methoxy-6-methylbenzoquinone	1,2,4-Trimethoxy-6-methylbenzene	82
1,4-Naphthoquinone	1,4-Dimethoxynaphthalene	94
2-Hydroxy-1,4-naphthoquinone	1,2,4-Trimethoxynaphthalene	67
2-Bromo-3-methyl-1,4-naphthoquinone	2-Bromo-1,4-dimethoxy-3-methylnaphthalene	88
Anthraquinone	1,4-Dimethoxyanthracene	92
1,4-Dihydroxy-9,10-anthraquinone	1,4,9,10-Tetramethoxyanthracene	66
3-Bromo-1-methoxy-9,10-anthraquinone	3-bromo-1,9,10-Trimethoxyanthracene	69
1,8-Dimethoxy-9,10-anthraquinone	1,8,9,10-Tetramethoxyanthracene	77

11.6.3 Reductive methylation of 1,4-benzoquinones

$\text{Na}_2\text{S}_2\text{O}_4$ (2.1 g, 12 mmol) is added to the quinone (2 mmol) and TBA-Br (0.075 g, 0.23 mmol) in THF (5 ml) and H_2O (2 ml) and the mixture is stirred for 15 min at room temperature. Aqueous KOH (5M, 1 ml) is added, followed after 5 min by Me_2SO_4 (5.5 g, 40 mmol) and the mixture is stirred at room temperature for 10 h. CH_2Cl_2 (5 ml) is then added and the organic phase is separated, washed with H_2O (2×5 ml), dried (MgSO_4), and evaporated to give the methoxy derivative, which is purified by chromatography on silica.

An intriguing use of a quaternary ammonium salt in a two-phase reaction is to be found with the regeneration of 1-benzyl-1,4-dihydronicotinamide by sodium dithionite in a biomimetic reduction of thiones to thiols [12]. The use of sodium dithionite in the presence of sodium carbonate for the 1,4-reduction of the pyridinium salts to 1,4-dihydropyridines is well established but, as both the dithionite and the pyridinium salts are soluble in water and the dihydropyridine and the thione are insoluble in the aqueous phase and totally soluble in the organic phase, it is difficult to identify the role of the quaternary ammonium salt in the reduction cycle. It is clear, however, that in the presence of benzyltriethylammonium chloride, the pyridine system is involved in as many as ten reduction cycles during the complete conversion of the thione into the thiol. In the absence of the catalyst, the thione is recovered quantitatively from the reaction mixture. As yet, the procedure does not appear to have any synthetic utility.

Viologen salts act as one-electron phase-transfer agents and, in conjunction with sodium dithionite which regenerates the bipyridinium radical cation, they have been used for the debromination of 1,2-dibromoalkanes to yield alkenes in variable yields [13–15]. Nitroarenes are reduced to anilines in high yield (>90%) under similar conditions [16], whereas conjugated nitroalkenes are converted into the oximes of the saturated ketones [17]; saturated aliphatic nitro compounds are not reduced by this process.

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11.7 HYDRIDOMETAL CARBONYL REDUCTIONS AND RELATED REACTIONS

As indicated in Chapter 8, the production of alkanes, as by-products, frequently accompanies the two-phase metal carbonyl promoted carbonylation of haloalkanes. In the case of the cobalt carbonyl mediated reactions, it has been assumed that both the reductive dehalogenation reactions and the carbonylation reactions proceed via a common initial nucleophilic substitution reaction and that a base-catalysed anionic (or radical) cleavage of the metal-alkyl bond is in competition with the carbonylation step [1]. Although such a mechanism is not entirely satisfactory, there is no evidence for any other intermediate metal carbonyl species.

The yields of ketones, isolated from the reductive debromination of α -bromo-ketones by dicobalt octacarbonyl under basic phase-transfer conditions are good (Table 11.13), but are improved (>95%) by the use of stoichiometric amounts of the quaternary ammonium catalyst. Somewhat unexpectedly, in the case of the reductive dehalogenation of secondary benzylic halides, the yields of the coupled alkanes are

TABLE 11.13
Selected examples of the reductive debromination of α -bromoketones

RCOCH ₂ Br	% yield	
	RCOCH ₃	RCO(CH ₂) ₂ COR
PhCOCH ₂ Br	23	55
2-NaphthylCOCH ₂ Br	66	0
4-PhC ₆ H ₄ COCH ₂ Br	64	0
4-BrC ₆ H ₄ COCH ₂ Br	69	28
4-MeOC ₆ H ₄ COCH ₂ Br	25	20
1-AdamantylCOCH ₂ Br	58	0

enhanced by higher pressures of carbon monoxide and by more dilute concentrations of aqueous sodium hydroxide than are required to promote the formation of the carboxylic acids [2]. This synthetic routine to the diarylethanes can be a viable proposition.

The higher yields of the coupled products from the reaction of the α -bromoacetophenones have been attributed to the differences in the two-phase distribution of the ions, compared with the other systems. The 1,4-diketone was isolated, as the major product, from the reductive debromination of α -bromocamphor.

11.7.1 Reductive debromination of α -bromoketones using dicobalt octacarbonyl

TEBA-Cl (0.11 g, 0.5 mmol) in aqueous NaOH (5M, 10 ml) is added with stirring under N₂ to Co₂(CO)₈ (0.03 g, 0.1 mmol) and the α -bromoketone (1.0 mmol) in PhH (10 ml). The mixture is stirred for a further 2 h and the organic phase is then separated, dried (MgSO₄), and evaporated under reduced pressure. The ketones are separated from the 1,4-diketones by chromatography on Florosil.

11.7.2 Synthesis of diarylethanes (Table 11.14)

A steel autoclave (500 ml) is charged with PhMe (100 ml), aqueous NaOH (20%, 150 ml), TEBA-Cl (7.2 g, 19 mmol), Co₂(CO)₈ (3.1 g, 9 mmol) and the benzyl halide

TABLE 11.14
Selected examples of the synthesis of 1,2-diarylethanes

ArCH(X)R	Reaction conditions	% yield of ArCH(R)CH(R)Ar
PhCH(Br)Me	11.7.2/30 °C	81
PhCH(Br)Et	11.7.2/35 °C	20 ^a
4-MeC ₆ H ₄ CH(Br)Me	11.7.2/35 °C	60
3-ClC ₆ H ₄ CH(Br)Me	11.7.2/35 °C	30 ^b
Ph ₂ CHCl	11.7.2/45 °C ^c	94
Ph ₂ CHBr	11.7.2/10 °C ^c	76

^a A mixture of phenylpropenes constitute the major yield of products. ^b + ca. 50% mixture of 3-ClC₆H₄Et and 3-ClC₆H₄CH=CH₂. ^c Under 1 atmos. pressure of CO.

(0.1 mol) under CO (5 atmos.). The mixture is stirred for 20 h at 30–35°C and the organic phase is then separated, washed with H₂O (3 × 25 ml), dried (Na₂SO₄), and evaporated to give the alkane.

In contrast with the cobalt carbonyl-mediated reactions, it is well established that the hydridoiron tetracarbonyl anion brings about the reductive dehalogenation of α -haloketones and benzyl halides, whereas the iron tetracarbonyl dianion promotes carbonylation to produce carboxylic acids or ketones (see Chapter 8) [3], for example, 1,2-bis(bromomethyl)benzene is reduced to *o*-xylene under homogeneous conditions by tetra-*n*-butylammonium hydridoiron tetracarbonyl, whereas it reacts under basic two-phase conditions with iron pentacarbonyl and tetra-*n*-butylammonium hydrogen sulphate to give a π -complex of 1,2-bismethidoquinone via the initial formation of the iron tetracarbonyl dianion [4].

The reactive anionic hydridometalcarbonyl complexes can be preformed from the neutral metal carbonyls using quaternary ammonium borohydrides either under homogeneous conditions or two-phase catalytic conditions [5] and are used in a range of reductive processes. The preparation of tetraethylammonium hydridotri-iron undecylcarbonyl is used as an illustrative example.

11.7.3 Preparation of hydridometal carbonyl reagents

Method A (homogeneous conditions): Fe₃(CO)₁₂ (0.5 g, 1.0 mmol) and TEA-BH₄ (0.14 g, 1.0 mmol) in CH₂Cl₂ (50 ml) are stirred at room temperature for 5 min until the initial green colour becomes purple. The solution is washed with H₂O (3 × 60 ml), dried (MgSO₄), and evaporated under vacuum to give TEA-HFe₃(CO)₁₁.

Method B (phase-transfer conditions): Fe₃(CO)₁₂ (0.5 g, 1.0 mmol) in CH₂Cl₂ (80 ml) and TEA-Br (0.31 g, 1.5 mmol) and NaBH₄ (0.38 g, 10.0 mmol) in H₂O (50 ml) are stirred at room temperature for 30 min. The dark red organic phase is separated and washed with H₂O (3 × 60 ml). The aqueous washings are extracted with CH₂Cl₂ (30 ml) and the combined organic solutions are dried (MgSO₄) and evaporated to give the TEA-HFe₃(CO)₁₁ (80%) [similar salts are obtained in 83% yield from Ru₃(CO)₁₂ and 70% from Mo(CO)₆].

The reductive dehalogenation of haloalkanes has also been achieved in high yield using polymer supported hydridoiron tetracarbonyl anion (Table 11.15). In reactions where the structure of the alkyl group is such that anionic cleavage is not favoured, carbonylation of the intermediate alkyl(hydrido)iron complex produces an aldehyde (see Chapter 8) [3].

TABLE 11.15

Polymer-supported metallohydride carbonyl dehalogenation reactions

Bromo compound	Product	% yield
PhCOCH ₂ Br	PhCOMe	90
Me(CH ₂) ₃ CHBrCO ₂ Me	Me(CH ₂) ₄ CO ₂ Me	81
PhCHBrPh	PhCH ₂ Ph	85
PhCHBrCHBrPh	<i>trans</i> -PhCH=CHPh	85
2-Bromocyclohexanone	cyclohexanone	92

11.7.4 Reductive dehalogenation of haloalkanes using polymer-supported hydridoiron tetracarbonyl anion

The polymer supported $\text{HFe}(\text{CO})_4^-$ ion (33 mmol), prepared according to procedure 8.4.3, is stirred with the haloalkane (11 mmol) in THF (50 ml) for 4 h at room temperature. The resin is separated by filtration and the solvent is evaporated under reduced pressure to yield the alkane.

A viable iron carbonyl-mediated reduction process converts acid chlorides and bromoalkanes into aldehydes [3, 6]. Yields are high, with the exception of nitrobenzoyl chloride, and the procedure is generally applicable for the synthesis of alkyl, aryl and α,β -unsaturated aldehydes from the acid chlorides. The reduction proceeds via the initial formation of the acyl iron complex, followed by hydride transfer and extrusion of the aldehyde (*cf.* Chapter 8).

11.7.5 Reduction of acid chlorides (Table 11.16)

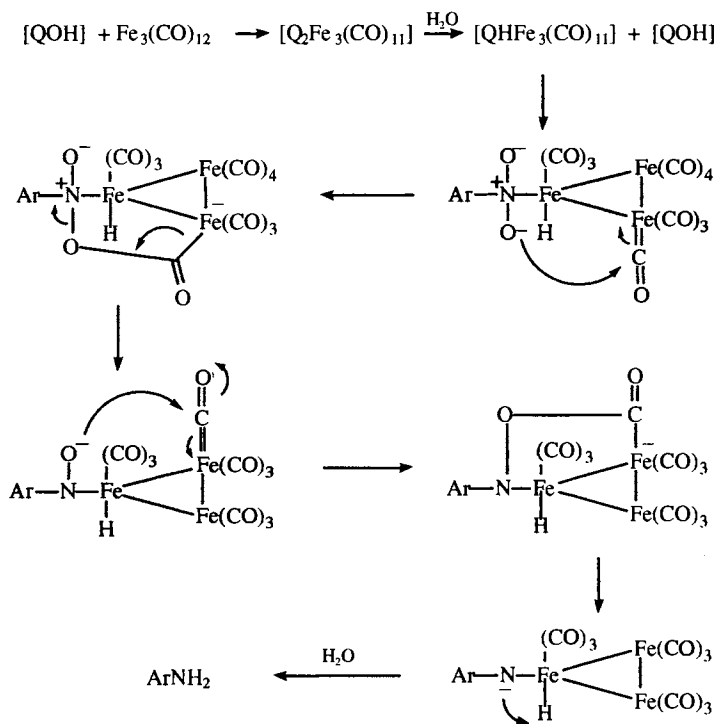
The acid chloride (2 mmol) in CH_2Cl_2 (8 ml) is added via a syringe to TMA- $\text{HFe}(\text{CO})_4$ (0.97 g, 4 mmol), preformed by the addition of $\text{Fe}(\text{CO})_5$ (7.0 g, 35.7 mmol) to KOH (7.0 g) and TMA-Br (7.5 g, 48.7 mmol) in H_2O (40 ml). The mixture is stirred at room temperature until the reduction is complete. The organic phase is separated, washed well with H_2O , and evaporated. The aldehyde is extracted from the residue with Et_2O .

Nitroarenes are reduced to anilines (>85%) under the influence of metal carbonyl complexes. In a two-phase system, the complex hydridoiron complex $[\text{HFe}_3(\text{CO})_{11}]^{2-}$ is produced from tri-iron dodecacarbonyl at the interface between the organic phase and the basic aqueous phase [7]. The generation of the active hydridoiron complex is catalysed by a range of quaternary ammonium salts and an analogous hydrido-manganese complex is obtained from dimanganese decacarbonyl under similar conditions [8]. Virtually no reduction occurs in the absence of the quaternary ammonium salt, and the reduction is also suppressed by the presence of carbon monoxide [9]. In contrast, dicobalt octacarbonyl reacts with quaternary ammonium fluorides to form complexes which do not reduce nitroarenes.

TABLE 11.16
Selected examples of the reduction of acid chlorides

Acid chloride	Reaction conditions	% yield of aldehyde
MeCOCl	11.7.5/3 h	100
$t\text{-BuCCOCl}$	11.7.5/1.5 h	80
$n\text{-C}_5\text{H}_{11}\text{COCl}$	11.7.5/1.25 h	99
$\text{cyclo-C}_6\text{H}_{11}\text{COCl}$	11.7.5/2.75 h	95
PhCOCl	11.7.5/1.25 h	91
$4\text{-BrC}_6\text{H}_4\text{COCl}$	11.7.5/1 h	80
PhCH=CHCOCl	11.7.5/1.75 h	22
2-FurylCOCl	11.7.5/4 h	90

The most probable mechanism for the reduction requires the initial nucleophilic attack by the hydridometal complex on the nitro group, followed by intramolecular cyclization and extrusion of carbon dioxide. Repetition of the cyclization and extrusion sequence, followed by proton transfer, leads to aniline (Scheme 11.6).



Scheme 11.6

Aniline has also been obtained (93%) from a homogenous reduction with preformed tetraethylammonium hydridotri-iron undecacarbonyl [10]. In this reduction, the yield is comparable, or superior, to that obtained when the more reactive iron pentacarbonyl or di-iron nonacarbonyl complex is used in the absence of a phase-transfer catalyst.

In many respects the apparently analogous reduction of nitroarenes with triruthenium dodecacarbonyl under basic phase-transfer conditions is superior to that of the iron carbonyl-mediated reductions. However, the difference in the dependence of the two processes on the concentration of the aqueous sodium hydroxide and the pressure of the carbon monoxide suggests that they may proceed by different mechanisms. Although the iron-based system is most effective under dilute alkaline conditions in the absence of carbon monoxide, the use of 5M sodium hydroxide is critical for the ruthenium-based system, which also requires an atmosphere of carbon monoxide [11]. The ruthenium-based reduction has been extended to the

nitroalkanes with some success but, with nitroarenes, the reduction is susceptible to steric hindrance.

In a manner analogous to the formation of the other hydridometal complexes, the tricarbonylhydridovanadate anion is easily produced from η^5 -cyclopentadienyl-vanadiumtetracarbonyl under basic phase-transfer catalytic conditions and it has been used in the reduction of nitro compounds and the reductive dehalogenation of a wide range of halides [12].

11.7.6 Reduction of nitroarenes

Method A (using iron complexes): $\text{Fe}_3(\text{CO})_{12}$ (0.25 g, 0.5 mmol) and the nitroarene (1.0 mmol) in PhH (10 ml) are stirred for 2 h with TEBA-Cl (0.02 g, 0.1 mmol) in aqueous NaOH (1M, 10 ml) at room temperature. The organic phase is separated and filtered through silica to give the aniline.

Method B (using ruthenium complexes): $\text{Ru}_3(\text{CO})_{12}$ (0.025 g, 0.03 mmol) in PhH (20 ml) and $\text{MeO}(\text{CH}_2)_2\text{OH}$ (5 ml) are added to TEBA-Cl (0.05 g, 0.25 mmol) in aqueous NaOH (5M, 10 ml) and the mixture is stirred for 1 h under an atmosphere of CO. The nitro compound (5.0 mmol) in PhH (5 ml) is added and stirring is continued until the reaction is complete. The aniline is isolated by the procedure described in 11.7.6.A (Table 11.17).

TABLE 11.17

Selected examples of the ruthenium promoted reduction of nitroarenes

Nitroarene	Reaction conditions	% yield of amine ^a
PhNO_2	11.7.6.B/9 h	100
4-MeC ₆ H ₄ NO ₂	11.7.6.B/8 h	94 (85)
4-MeOC ₆ H ₄ NO ₂	11.7.6.B/7 h	84 (92)
4-ClC ₆ H ₄ NO ₂	11.7.6.B/3 h	100 (88)
4-PhCOC ₆ H ₄ NO ₂	11.7.6.B/4.5 h	100
2,6-Me ₂ C ₆ H ₃ NO ₂	11.7.6.B/25 h	8
2-FC ₆ H ₄ NO ₂	11.7.6.B/20 h	95
<i>n</i> -C ₇ H ₇ NO ₂	11.7.6.B/17 h	85

^a Yields given in parentheses relate to $\text{Fe}_3(\text{CO})_{12}$ promoted reductions [8].

11.7.7 Synthesis of tetraethylammonium hydrodotri-iron decacarbonyl

$\text{Fe}(\text{CO})_5$ (160.5 g, 0.82 mol) and Et_3N (60 g, 0.59 mol) in degassed H_2O (240 ml) are stirred at 80°C for ca. 15 h. The mixture is cooled and the precipitated $\text{Et}_3\text{NH}[\text{HFe}_3(\text{CO})_{10}]$ (ca. 100 g) is collected and washed with H_2O (50 ml). TEA-Cl (8.0 g, 49.3 mmol) in CH_2Cl_2 (50 ml) is added to the complex (22 g, 38 mmol) and the mixture is stirred at room temperature for 30 min. The solvent is removed under reduced pressure and the crude TEA- $\text{HFe}_3(\text{CO})_{10}$ is recrystallized from MeOH.

11.7.8 Reduction of nitroarenes with TEA-HFe₃(CO)₁₀

The nitroarene (5 mmol) in dry THF (10 ml) is added dropwise to TEA-HFe₃(CO)₁₀ (3.0 g, 5 mmol) in dry THF (30 ml) and the mixture is heated at 50°C for 2 h and then cooled and acidified with aqueous HCl (5M). The acidic solution is washed with Et₂O (2 × 25 ml) and the aqueous phase is then made alkaline with aqueous NaOH (5M) and extracted with Et₂O (3 × 25 ml). The combined extracts are dried (Na₂SO₄) and evaporated under vacuum to give the aniline.

The mechanism and rate of reduction of nitroarenes by cluster rhodium/cobalt carbonyls under basic conditions and catalysed by dodecyltrimethylammonium chloride has been reported [13].

Desulphurization of thiols has been accomplished in high yield under phase-transfer conditions using tri-iron dodecacarbonyl (or dicobalt octacarbonyl). The mechanism proposed for the formation of the alkanes and the dialkyl sulphide by-products involves a one electron transfer to the thiol from the initially formed quaternary ammonium hydridoiron polycarbonyl ion pair [14]. Similar one electron transfers have been postulated for the key step in the cobalt carbonyl promoted reactions, which tend to give slightly higher yields of the alkanes (Table 11.18).

TABLE 11.18

Selected examples of the desulphurization of benzylic thiols

ArCR ¹ R ² SH				% yield using	
				Fe ₃ (CO) ₁₂	Co ₂ (CO) ₈
Ar = 2-MeC ₆ H ₄	R ¹ = H	R ² = H	1,2-Me ₂ C ₆ H ₄	87 ^a	—
4-MeC ₆ H ₄	H	H	1,4-Me ₂ C ₆ H ₄	58 ^b	79 ^c
4-MeOC ₆ H ₄	H	H	4-MeOC ₆ H ₄ Me	73 ^d	82 ^e
Ph	Ph	H	Ph ₂ CH ₂	82 ^f	84 ^g
Ph	Ph	Ph	Ph ₃ CH	65	82

^a + 10% (2-MeC₆H₄CH₂)₂S and 3% (2-MeC₆H₄CH₂)₂S₂. ^b + 4% (4-MeC₆H₄CH₂)₂S and 5% (4-MeC₆H₄CH₂)₂S₂. ^c + 3% of each of (4-MeC₆H₄CH₂)₂S and (4-MeC₆H₄CH₂)₂S₂. ^d + 12% (4-MeOC₆H₄CH₂)₂S. ^e + 11% (4-MeOC₆H₄CH₂)₂S₂. ^f + 11% Ph₃CH, 5% (Ph₂CH₂)₂S and 1% (Ph₂CHS)₂. ^g + 10% Ph₃CH, 2% (Ph₂CH₂)₂S and 4% (Ph₂CHS)₂.

11.7.9 Desulphurization of thiols

A two-phase system of aqueous NaOH (5M, 25 ml) and PhH (25 ml) with TBA-HSO₄ (0.34 g, 1.0 mmol) is degassed for 30 min. The metal carbonyl (2.0 mmol) is added and the mixture is stirred for 4 min before the thiol (2 mmol) is introduced. The mixture is then stirred at 60°C for ca. 12 h. The organic phase is separated, washed with H₂O (2 × 25 ml), dried (MgSO₄), and fractionally distilled to give the alkanes.

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11.8 MISCELLANEOUS REDUCTION PROCEDURES

Although formamidine sulphinic acid, which is readily obtained by the oxidation of thiourea with hydrogen peroxide, is cited as a powerful reducing agent, it has been little used in phase-transfer catalysed reductions. It can be solublized by quaternary 'onium salts in organic solvents under basic conditions [1] reducing disulphides to thiols and converting *N*-tosylsulphinimines into thioethers. The latter reduction has also been achieved via the initial reaction of the sulphinimine with dichlorocarbene, generated by Makosza's method (see Chapter 8), and the subsequent extrusion of the imine [2].

TABLE 11.19

Selected examples of the conversion of sulphilimines and sulfoximines into disulphides^a

R ¹ S(=NX)R ²		Reaction conditions	% yield
<i>Sulphilimines, X = H</i>			
R ¹ = Ph	R ² = Ph	11.8.1/2 h	94
Ph	4-ClC ₆ H ₄	11.8.1/2 h	99
Ph	4-MeC ₆ H ₄	11.8.1/2 h	70
Ph	4-O ₂ NC ₆ H ₄	11.8.1/1 h	76
<i>N-Tosylsulphilimines, X = Tos</i>			
R ¹ = Ph	R ² = Ph	11.8.1/1.5	58 ^b
Ph	4-ClC ₆ H ₄	11.8.1/6 h	99 ^c
Ph	4-MeC ₆ H ₄	11.8.1/6 h	91 ^c
Ph	4-O ₂ NC ₆ H ₄	11.8.1/6 h	22 ^c
Ph	4-MeCOC ₆ H ₄	11.8.1/6 h	81 ^c
Ph	Me	11.8.1/4.5 h	84
Ph	Et	11.8.1/2 h	20
Ph	PhCH ₂	11.8.1/2 h	29
<i>n</i> -Bu	<i>n</i> -Bu	11.8.1/3 h	9
<i>Sulfoximines, R¹S(=O)(=NH)R²</i>			
R ¹ = Ph	R ² = Ph	11.8.1/3 h	82
Ph	Me	11.8.1/1 h	28
<i>n</i> -Bu	<i>n</i> -Bu	11.8.1/2 h	9

^a Using 0.1 mol equivalent of catalyst. ^b 82% with 0.4 mol equivalent of catalyst after 6 h. ^c Using 0.4 mol equivalent of catalyst.

Sulphoxides and sulfoximines are reduced to thioethers by similar reaction sequences [3, 4]. In most cases, the yields of the thioethers are higher (>70%) from the diaryl compounds, than from dialkyl or aryl alkyl derivatives but, when the reductions are conducted in an excess of chloroform, the yields of the thioethers are diminished [3]. This observation suggests that the thioethers are reacting with dichlorocarbene and that the dialkyl and aryl alkyl compounds are more susceptible than the diaryl derivatives (Table 11.20).

Compared with the sulphinimines, the *N*-tosylsulphinimines are less readily reduced and, to obtain acceptable yields, it is necessary to use larger amounts of catalyst. This suggests that the *N*-tosyl derivatives may be hydrolysed to the sulphinimines prior to the electrophilic attack by the carbene.

TABLE 11.20
Selected examples of the deoxygenation of sulphoxides

R ¹ SOR ²		Added CHCl ₃	% yield of sulphide
R ¹ = Ph	R ² = Ph	1.25 mmol	96
4-MeC ₆ H ₄	4-MeC ₆ H ₄	1.20 mmol	98
4-ClC ₆ H ₄	4-ClC ₆ H ₄	1.10 mmol	89
4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	1.30 mmol	89
4-O ₂ NC ₆ H ₄	Ph	1.30 mmol	78
Me	Ph	3.00 mmol	80
<i>t</i> -Bu	Ph	1.00 mmol	71
<i>n</i> -Bu	<i>n</i> -Bu	3.00 mmol	78
<i>t</i> -Bu	<i>t</i> -Bu	0.54 mmol	65 ^a
PhCH ₂	PhCH ₂	1.30 mmol	20

^a 37% when 1.3 moles of CHCl₃ is used.

11.8.1 Reduction of sulphinimines and sulfoximines using dichlorocarbene

Aqueous KOH (50%, 15 ml) and CHCl₃ (1 ml, 12.5 mmol) are added to the sulphinimine (or sulfoximine) (1 mmol) and TEBA-Cl (22.9 mg, 0.1 mmol) in CH₂Cl₂ (5 ml). The mixture is stirred at room temperature (Table 11.19). The aqueous phase is separated and extracted with CH₂Cl₂ (3 × 20 ml). The combined organic solutions are dried (Na₂SO₄) and evaporated to give the thioether, which is purified by chromatography on silica.

11.8.2 Reduction of sulphoxides to thioethers using dichlorocarbene (Table 11.20)

Aqueous KOH (50%, 7 ml) is added to the sulphoxide (1 mmol) and TEBA-Cl (0.025 g, 0.11 mmol) in CHCl₃ (1–3 mmol) and CH₂Cl₂ (5 ml), and the mixture is stirred at room temperature for 20 h. The thioether is isolated as described in 11.8.1.

Aliphatic and aromatic sulphonic acids have been reduced to symmetrical disulphides in almost quantitative yields using potassium iodide and ethyl polyphosphate

(tetraphosphorus deca-oxide, or polyphosphoric acid) in the presence of tetra-*n*-butylammonium iodide [4].

11.8.3 Reduction of sulphonic acids to disulphides

KI (8.0 g, 48 mmol) and TBA-I (0.58 g, 1.5 mmol) are added to the sulphonic acid (6 mmol) and ethyl polyphosphate or polyphosphoric acid (48 mmol) [or P_4O_{10} (36 mmol)] in the appropriate solvent (20 ml) ($CHCl_3$ for ethyl polyphosphate; sulfolane for polyphosphoric acid; MeCN for P_4O_{10}) and stirred under reflux for *ca.* 5 h. H_2O (10 ml) is added and the mixture is refluxed for a further 1 h and then poured into PhH (100 ml). The organic phase is separated, washed with H_2O (3×50 ml) and aqueous $Na_2S_2O_3$ (0.5M, 2×100 ml), dried (Na_2SO_4), and evaporated to yield the disulphide.

The catalytic effect of tetra-*n*-butylammonium fluoride in the homogeneous reduction of heterocyclic *N*-oxides and nitroarenes by hexamethyldisilane in tetrahydrofuran can occur with EXPLOSIVE violence, but can be controlled by the slow addition of the disilane to the *N*-oxide (or nitroarene) and tetra-*n*-butylammonium fluoride to yield the parent heterocycle (>70%) (or azobenzene 84%). In a similar manner, azoxybenzene is converted into azobenzene (95%), and 4-nitropyridine-1-oxide, is reduced to azoxypyridine-1,1'-dioxide (78%), with minor amounts of azopyridine-1,1'-dioxide and azopyridine-1-oxide [5, 6].

11.8.4 Deoxygenation of N–O functions using hexamethyldisilane in the presence of TBA-F

The $Me_3SiSiMe_3$ (3.55 g, 22 mmol) in dry THF (10 ml) is added SLOWLY with stirring to the pyridine 1-oxide (or nitroarene) (20 mmol) and TBA-F (0.26 g, 1 mmol) in dry THF (50 ml) at such a rate that the temperature does not exceed 35°C. The mixture is then stirred at 18–35°C (Table 11.21).

Nitrones and amine *N*-oxides are deoxygenated by a stoichiometric amount of benzyltriethylammonium tetrathiomolybdate to yield imines and amines, respectively (>80%) [7]. Nitro groups and sulfoxides are not reduced under these reaction conditions.

TABLE 11.21
Deoxygenation of heteroaromatic *N*-oxides

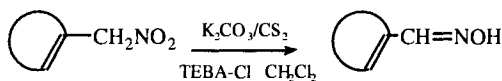
<i>N</i> -Oxide	Reaction conditions	% yield
Pyridine <i>N</i> -oxide	11.8.4/3 h/24–35°C	90
3-Methylpyridine <i>N</i> -oxide	11.8.4/7 h/18–23°C	85
4-Dimethylaminopyridine <i>N</i> -oxide	11.8.4/8 h/24–30°C ^a	84
3-Cyanopyridine <i>N</i> -oxide	11.8.4/24 h/24–26°C ^{a,b}	51
Quinoline <i>N</i> -oxide	11.8.4/16 h/24–35°C ^c	72
Isoquinoline <i>N</i> -oxide	11.8.4/3 h/23–26°C	92

^a Using 2 mmol TBA-F ^b Using 44 mmol $Me_3SiSiMe_3$. ^c Using 10 mmol TBA-F.

11.8.5 Deoxygenation of nitrones and *N*-oxides

The nitrone (or *N*-oxide) (1 mmol) in MeCN (2 ml) is added to TEBA-MoS₄ (0.5 g, 1.2 mmol) in MeCN (5 ml) and the mixture is stirred at 25 °C for 12–72 h. The solvent is evaporated and the residue is extracted with Et₂O (3 × 15 ml). Evaporation of the dried ethereal solution gives the deoxygenated product [e.g. 60% PhCH=NPh (22 h); 86% PhCH=NCH₂Ph (72 h); 72% 4-ClC₆H₄CH=NPh (27 h); 88% 4-NO₂C₆H₄CH=NPh (12 h); 83% 2-naphthyl-CH=NPh (21 h); 74% *N*-methylmorpholine (72 h)].

Allylic nitro compounds are reduced by carbon disulphide under mild basic catalytic conditions to yield the conjugated oximes (Scheme 11.7) [8]. The reaction is sensitive to the amount of base used, and benzyltriethylammonium chloride appears to be a better catalyst than tetra-*n*-butylammonium bromide or hydrogen sulphate. Saturated nitro compounds are not reduced under these conditions.



Scheme 11.7

During these reactions, nitriles are also formed as by-products and it is probable that they result from dehydration of the oxime by the carbon disulphide under the phase-transfer catalytic conditions [9] (see Chapter 9). Under modified conditions, it is possible to carry out a one-pot high-yielding conversion of the nitro compounds into the nitriles [10].

11.8.6 Reductive conversion of allylic nitro compounds into conjugated oximes

The nitro compound (0.1 mol) TEBA-Cl (2.28 g, 10 mmol) anhydrous K₂CO₃ (6.9 g, 50 mmol) in CH₂Cl₂ (100 ml) containing H₂O (0.36 ml) are stirred at room temperature for 15 min. CS₂ (9.02 g, 0.15 mol) is added in one portion and the mixture stirred for a further period (Table 11.22). The mixture is filtered through Celite and evaporated to yield the oxime, which is purified by chromatography.

Hydride ion transfer from formic acid and its salts finds widespread application in the reduction of organic substrates, but limited use has been made of the procedure under phase-transfer catalytic conditions. However in the presence of a ruthenium complex catalyst, it is possible to selectively reduce the C=C bonds of conjugated ketones with sodium formate [11]. The rate of reduction is fastest with tetrahexylammonium hydrogensulphate and Aliquat; the complete reduction of chalcone being effected within one hour, whereas with benzyltriethylammonium chloride only *ca.* 15% reduction is observed after two hours under similar conditions.

It has been postulated that direct hydride transfer from the formate ion to the ketone does not occur, but that interaction of the quaternary ammonium formate with

TABLE 11.22
Reductive conversion of allylic nitro compounds into conjugated oximes

RCH ₂ NO ₂	Reaction conditions	% yield of RCH=NOH
R = cyclohex-1-enyl	11.8.6/7 h	52
4-Methylcyclohex-1-enyl	11.8.6/8 h	60
6-Methylcyclohex-1-enyl	11.8.6/5 h	68
4- <i>t</i> -Butylcyclohex-1-enyl	11.8.6/14 h	60
6-Phenylcyclohex-1-enyl	11.8.6/25 h	51
2-Phenylcyclohex-1-enyl	11.8.6/25 h	79
2-Isopropylcyclohex-1-enyl	11.8.6/25 h	25
cyclohept-1-enyl	11.8.6/24 h	60
cyclooct-1-enyl	11.8.6/7 d	60
cyclododec-1-enyl	11.8.6/6.5 d	56
3,4-Dihydronaphth-1-yl	11.8.6/8 h	60

the bis(triphenylphosphine) complex of ruthenium chloride leads to the initial formation of a ruthenium hydride species (*cf.* the reduction of the C=C bonds of conjugated enones with tetraethylammonium hydridotri-iron decarbonyl [6]). Triphenylphosphine palladium(0) complexes can be used in place of the ruthenium salt; overall yields for the 1,4-reduction of benzal acetone, ethyl cinnamate, and of a series of chalcones are generally >90%, with 100% regioselectivity.

11.8.7 Ruthenium chloride mediated reduction of conjugated ketones

The conjugated ketone (5 mmol) and RuCl₂(Ph₃P)₃ (0.05 g, 5.2 mmol) are warmed in degassed 1,2-dichlorobenzene (19 ml) until a clear orange-brown solution is obtained. HCO₂Na (3.4 g, 50 mmol) and THA-HSO₄ (0.05 g, 0.1 mmol) in H₂O (20 ml) are added and the mixture is stirred under N₂ at *ca.* 10°C for 1 min. The organic phase is separated, washed with H₂O (2 × 25 ml), dried (MgSO₄), and evaporated to yield the reduced product.

Quaternary ammonium salts aid the transfer of the hypophosphite anion in the palladium-catalysed reduction of, for example, alkynes to alkenes, nitroarenes to aminoarenes, and in the hydrogenolysis of tetrazolyl aryl ethers to phenols [12–14]. It has been demonstrated that the hydrogenolysis is ineffective when preformed tetra-*n*-butylammonium hypophosphite is employed in a dry homogenous organic solvent [13, 14]. For optimum hydrogen transfer, the concentration of hypophosphite relative to the substrate must be controlled at a low level and this is most effectively accomplished with a two-phase system.

Reductive metallation of aldehydes (but not ketones) by tri-*n*-butyl-(trimethylsilyl)stannane to yield α-hydroxystannanes is catalysed by tetra-*n*-butylammonium cyanide [15]. Other phase-transfer catalysts are not as effective and solvents, other than tetrahydrofuran, generally give poorer conversions. Use of a chiral catalyst induced 24% ee with 3-phenylpropanal.

11.8.8 α -Hydroxystannanes (Table 11.23)

Bu₃SnSiMe₃ (0.3 mol) in THF (4 ml) is added to the aldehyde (0.2 mol) and TBA-CN (1.61 g, 6 mmol) in THF (5 ml) at room temperature and the mixture is stirred for *ca.* 2 h. NH₄Cl (sat. soln, 4 ml) is added and the reaction mixture is extracted with Et₂O (2 \times 5 ml). The extracts are washed with H₂O (2 \times 5 ml) and brine (5 ml) and evaporated to yield the stannane and its *O*-silyl derivative, which are separated by chromatography from silica.

TABLE 11.23

Selected examples of α -hydroxystannanes from aldehydes

RCHO	Overall yield	Ratio of α -silyloxystannane: α -hydroxystannane
(HCHO) _n	80	>50 : 1
<i>t</i> -BuCHO	71 ^a	>50 : 1
<i>n</i> -C ₇ H ₁₅ CHO	80	3 : 1
cyclo-C ₆ H ₁₁ CHO	68 ^b	>50 : 1
Ph(CH ₂) ₂ CHO	82	3 : 1
PhCHO	85 ^c	4.6 : 1
4-MeOC ₆ H ₄ CHO	98 ^d	>50 : 1
4-CF ₃ C ₆ H ₄ CHO	15 ^e	>50 : 1

^a 5 h at -78°C. ^b 1 h at -20°C. ^c 35 min at 10°C in PhH. ^d 45 min at 10°C in PhH. ^e 24 h at 23°C in PhH.

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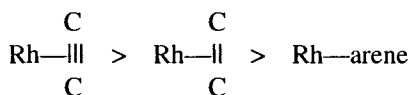
11.9 CATALYTIC HYDROGENATION UNDER PHASE-TRANSFER CATALYTIC CONDITIONS

In a different approach to those described in earlier sections, quaternary ammonium salts are used to solubilize hydrogenation catalysts either in the organic substrate or

in an organic solution of the substrate. The rate of hydrogenation is enhanced, some regiospecificity may be induced in the reduction, and the lifetime of the metal catalyst may be increased by prevention of precipitation of the zero-valent metal. In many respects, the hydrogenation catalysts display the properties of established homogeneous catalysts, such as Wilkinson's catalyst. In the presence of Aliquat, rhodium chloride is transported into organic solvents, as the ion pair [MTOA-RhCl₄] [1, 2], and alkenes, alkynes and arenes can be efficiently hydrogenated under one atmosphere pressure of hydrogen at room temperature [3] (Table 11.24). The procedure is particularly valuable for the hydrogenation of arenes, for which high temperatures and pressures are normally required, and for which irreproducible and erratic results are frequently obtained.

The exact structural nature of the hydrogenation catalyst has not been defined. It is significant, however, that presaturation of the organic phase with hydrogen is necessary to eliminate a long induction period and that, although the water does not provide the hydrogen for the reduction, the hydrogenation is totally ineffective in the absence of water. In the absence of the ammonium salt, rhodium metal separates during the hydrogenation.

The mechanism for the hydrogenation probably involves Rh- π interaction with the unsaturated systems. The selectivity of competitive hydrogenation experiments has established the relative order of the interaction forces [3]:



The isolation of benzene and cyclohexane from chlorobenzene and thiophenol, and cyclohexane from fluorobenzene, suggests the preferential reductive cleavage of the substituent prior to hydrogenation of the ring. However, fluorocyclohexane decomposes slowly to cyclohexene, which could give rise to the cyclohexane; higher yields of fluorocyclohexane are obtained at lower temperatures.

The aryl rings of acetophenone and methyl benzoate are preferentially hydrogenated, with only minor reduction of the substituents. In contrast, hydrogenation of nitrobenzene, under essentially the same conditions, produces aniline and nitrocyclohexane in *ca.* 9:1 ratio, with an overall conversion of >79%. This observation has additional significance when compared with the hydrogenation of the nitro derivative of vinylbenzene (Table 11.25). In all cases, it is the C=C bond which is hydrogenated and, only after a prolonged reduction time, is 1-nitro-2-phenylethene completely reduced to the aminoethane [4].

11.9.1 RuCl₃-catalysed selective hydrogenation of nitro compounds

The nitro compound (1 mmol) in the appropriate solvent (0.5 ml), with Aliquat (22 mg, 0.55 mmol) and RuCl₃·3H₂O (10 mg, 0.04 mmol) in H₂O (0.5 ml) is hydrogenated under 1 atmos. pressure H₂. The organic phase is separated, washed with H₂O (2 × 5 ml), dried (MgSO₄), and evaporated to yield the hydrogenated product.

TABLE 11.24

Selected examples of the RuCl_3 -catalysed hydrogenation of arenes

Substrate	% conversion	Products (% ratio)
PhH	51	cyclo- C_6H_{12} (100%)
PhMe	16	cyclo- $\text{C}_6\text{H}_{11}\text{Me}$ (100%)
PhEt	13	cyclo- $\text{C}_6\text{H}_{11}\text{Et}$ (100%)
PhF	72	cyclo- $\text{C}_6\text{H}_{11}\text{F}$ (39%), cyclo- C_6H_{12} (59%), cyclo- C_6H_{10} (2%)
PhCl	74	cyclo- C_6H_{12} (78%), PhH (22%)
PhOH	56	cyclohexanone (78%), cyclo- $\text{C}_6\text{H}_{11}\text{OH}$ (27%), cyclo- C_6H_{12} (6%)
PhSH	27	PhH (69%), cyclo- C_6H_{12} (28%), cyclo- C_6H_{10} (3%)
PhNMe ₂	71	cyclo- $\text{C}_6\text{H}_{11}\text{NMe}_2$ (100%)
PhOMe	55	cyclo- $\text{C}_6\text{H}_{11}\text{OMe}$ (100%)
PhCOMe	87	cyclo- $\text{C}_6\text{H}_{11}\text{COMe}$ (41%), cyclo- $\text{C}_6\text{H}_{11}\text{CH(OH)Me}$ (43%), PhCH(OH)Me (14%)
PhCO ₂ Me	70	cyclo- $\text{C}_6\text{H}_{11}\text{CO}_2\text{Me}$ (89%), cyclo- $\text{C}_6\text{H}_{11}\text{CH}_2\text{OH}$ (10%), PhCH ₂ OH (1%)
PhCH=CH ₂	100	PhEt (94%), cyclo- $\text{C}_6\text{H}_{11}\text{Et}$ (6%)
PhC≡CPh	19	<i>cis</i> -PhCH=CHPh (78%), <i>trans</i> -PhCH=CHPh (22%)
Naphthalene	34	Tetralin (99%), <i>cis</i> -decalin (1%)

TABLE 11.25

Selective hydrogenation of unsaturated nitro compounds

Substrate	Reduction conditions	% yield (% ratio of product)
PhNO ₂	11.9.1/6 h ^a	70 (90%, PhNH ₂ ; 10%, cyclo- $\text{C}_6\text{H}_{11}\text{NH}_2$)
PhCH=CHNO ₂	11.9.1/22 h ^a	17 (100%, Ph(CH ₂) ₂ NO ₂)
3-O ₂ NC ₆ H ₄ CH=CHCO ₂ Me	11.9.1/5.5 h ^b	55 (100%, 3-O ₂ NC ₆ H ₄ (CH ₂) ₂ CO ₂ Me
3-O ₂ NC ₆ H ₄ CH=CHCOMe	11.9.1/4 h ^c	78 (100%, 3-O ₂ NC ₆ H ₄ (CH ₂) ₂ COMe)
3-O ₂ NC ₆ H ₄ CH=CH ₂	11.9.1/7 h ^b	70 (100%, 3-O ₂ NC ₆ H ₄ Et)

^a In CH_2Cl_2 , ^b In MeNO_2 , ^c In CHCl_3 .

Rhodium(III) complexes [e.g. $(i\text{-Pr}_3\text{P})_2\text{Rh(H)Cl}_2$] in the presence of quaternary ammonium salts are excellent catalysts for the hydrogenolysis of chloroarenes under mild conditions [5]; other labile substituents are unaffected. Hydrodehalogenation of haloaryl ketones over a palladium catalyst to give acylbenzenes is also aided by the addition of Aliquat [6]. In the absence of the phase-transfer catalyst, or when the hydrogenation is conducted in ethanol, the major product is the corresponding alkylbenzene, which is also produced by hydrodehalogenation of the halobenzyl alcohols.

Selective hydrogenation of $\text{C}=\text{C}$ bonds of conjugated ketones, without concomitant reduction of the carbonyl group, is achieved under mild conditions using the

water-soluble hydrogenation catalyst $K_3[Co(CN)_5H]$, which is solubilized in organic solvents by the addition of a quaternary ammonium salt [7]. The addition of the phase-transfer catalyst controls the product distribution, for example, sorbates are hydrogenated preferentially to yield *trans*-hex-3-enoates [8] and hydrogenation of but-3-en-2-one and 3-methylbut-3-en-2-one gives butanone (60%) and 3-methylbutan-2-one (85%), whereas carvone produces a 6:1 ratio of *trans*- and *cis*-menth-8(9)-en-2-ones in a 93% overall yield [7].

Partial hydrogenation of conjugated dienes to alkenes, under similar conditions, requires less catalyst than for the unsaturated ketones and appears to be dominated by 1,4-addition, for example, hydrogenation of 2,3-dimethylbuta-1,3-diene produces a 1:4 mixture of 2,3-dimethylbut-1- and -2-ene, whereas *trans*-penta-1,3-diene is exclusively hydrogenated to *trans*-pent-2-ene [9]. However, hydrogenation of *trans*-penta-1,3-diene labelled by deuterium at the 1-position indicates that 1,2- and 1,4-hydrogenation occurs to an equal extent. Steric factors control the rate of hydrogenation: 1,4-diphenylbuta-1,3-diene, 2,5-dimethylhexa-2,4-diene and, surprisingly, 2-methylbut-1-en-3-yne are not hydrogenated. Additionally, it is curious that partial hydrogenation of 2-methylpenta-1,3-diene and 4-methylpenta-1,3-diene produces the same ratio (27:73) of *trans*-2-methylpent-3-ene and 2-methylpent-2-ene.

Cyclohexa-1,3-diene is readily hydrogenated to cyclohexene, but cycloheptatriene is hydrogenated more slowly to give a mixture of cycloheptene and cyclohepta-1,3- and 1,4-diene. Further hydrogenation of the conjugated diene is extremely slow. Cyclohepta-1,4-diene and cyclo-octatetraene are not hydrogenated.

11.9.2 Hydrogenation of conjugated dienes

A closed hydrogenation system containing $CoCl_2 \cdot 6H_2O$ (1.56 g, 6.6 mmol), NaOH (0.27 g) and TEBA-Cl (0.23 g, 1 mmol) in H_2O (40 ml) is repeatedly evacuated and filled with H_2 until a constant pressure of H_2 is maintained. KCN (2.22 g) and KCl (1.08 g) in H_2O (20 ml) are added and the solution is stirred for 30 min. The diene (20 mmol) in PhH (20 ml) is added and the mixture is stirred under H_2 (one atmos). On completion of the reaction, the organic phase is separated, washed with H_2O (2×10 ml), dried ($MgSO_4$), and fractionally distilled to yield the alkene.

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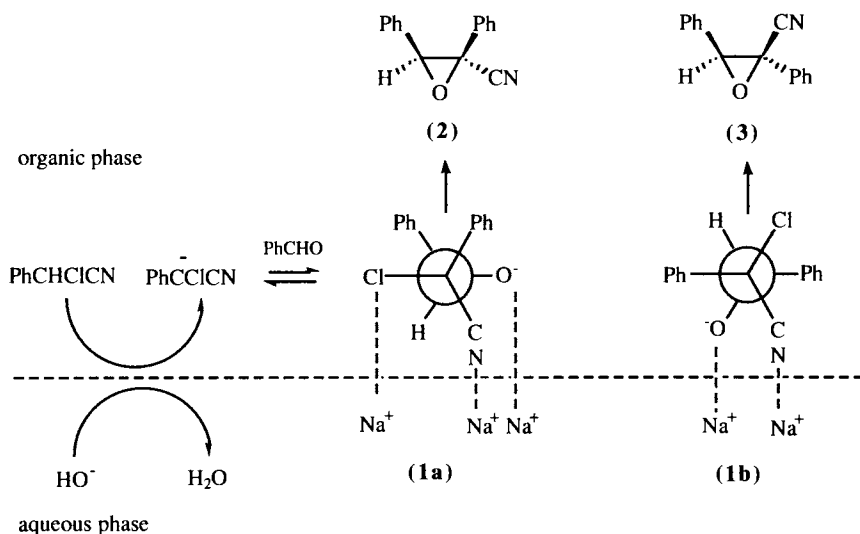
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- 12 -

Stereoselective Control in Phase-transfer Catalysed Reactions

12.1 INTRODUCTION

A degree of stereoselective control of the course of a reaction, which is absent or different from that prevalent when the reaction is conducted in the absence of quaternary ammonium salts, may be achieved under 'standard' phase-transfer catalysed reaction conditions. The reactions, which are influenced most by the phase-transfer catalyst, are those involving anionic intermediates whose preferred conformations or configurations can be controlled by the cationic species across the interface of the two-phase system. For example, in the base-catalysed Darzens condensation of aromatic aldehydes with α -chloroacetonitriles to produce oxiranes (Section 6.3), the intermediate anion may adopt either of the two conformations, **(1a)** or **(1b)** which are stabilized by interaction across the interface by the cations (Scheme 12.1) [1-4].



Scheme 12.1

Stereoisomers are also obtained from chloroacetonitrile and asymmetrically substituted ketones [5] and chloromethylsulphones react specifically with aldehydes to yield only the *trans*-substituted oxiranes [6].

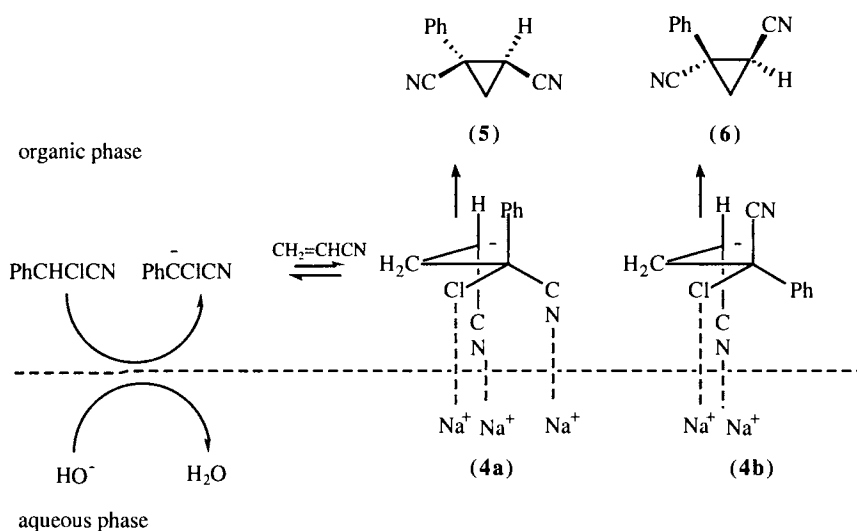
Steric interaction between the two phenyl groups would normally cause conformation (**1b**) to be thermodynamically more stable than (**1a**), but the greater interfacial interaction of the anion (**1a**) effectively eliminates the steric energy differences between (**1a**) and (**1b**) and almost equal amounts of the oxiranes (**2**) and (**3**) are obtained (Table 12.1). Addition of the phase-transfer catalyst leads to diffusion of the intermediate anions from the interface leading to the predominant formation of the 'trans' oxirane (**3**). The significance of the stabilizing effects of the interfacial interactions on (**1a**) and (**1b**) is well illustrated by the observation that, even in the absence of the phase-transfer catalyst, there is a change to the preferential formation of the 'trans' oxirane (**3**) when dilute alkaline solutions are used (Table 12.1). An analogous control of the stereochemistry of the catalysed ring closure has been noted for the reaction of aldehydes and ketones with 4-(chloromethylsulphonyl)toluene [3]. The reaction is highly stereospecific with aldehydes effectively forming only one diastereoisomer whereas, with asymmetric ketones, the *E*-isomers predominate with up to 23% ee.

TABLE 12.1
Stereochemical control of Darzen's reaction of α -chlorophenylacetonitrile with benzaldehyde by phase-transfer catalysts

Solvent system	Ratio (2):(3) (Scheme 12.1)	
	Without catalyst	With catalyst
PhH – 50% aq. NaOH	52 : 48	11 : 89
PhH – solid KOH	59 : 41	10 : 90
PhH – 17% aq. NaOH	6 : 94	2 : 98

Although the effect of quaternary ammonium salts on the stereochemistry of the two-phase condensation reaction of α -chloroacetonitrile with acrylonitriles to form cyclopropanes [4, 7] is not as pronounced as with the Darzens reaction, it can be rationalized in an analogous manner (Scheme 12.2). In the absence of the catalyst, the more highly stabilized anion (**4a**) is favoured leading to the preferential production of the 'cis' isomer (**5**). As with the Darzens reaction, addition of the catalyst causes diffusion of the anions (**4a**) and (**4b**), as ion-pairs, into the bulk of the organic phase where their relative stabilities are similar and a more equal ratio of the two isomeric cyclopropanes (**5**) and (**6**) results (Table 12.2).

The regiospecificity of the exclusive *O*-acylation [8] and *O*-phosphorylation [9] of β -dicarbonyl compounds (Chapter 3) also illustrates the effect of phase-transfer catalysts on the stereochemical course of reactions. Similarly, directed reduction of β -hydroxy ketones using tetramethylammonium trisacetoxyborohydride leads to the preferential formation of the 'anti' dihydroxy system in high yield with a stereoselectivity >95% [10] (Section 11.4).



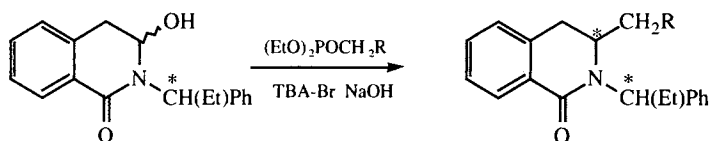
Scheme 12.2

TABLE 12.2

Effect of phase-transfer catalysts on the stereochemical formation of cyclopropanes

Solvent system	Ratio (5):(6)	
	Without catalyst	With catalyst
PhH – 50% aq. NaOH	93 : 7	60 : 40
PhH – solid KOH	90 : 10	51 : 41

Stereochemical control of a reaction can also be achieved using non-chiral catalysts, when a chiral centre already exists in the reactant, as for example in the reaction of cyano- or methoxycarbonylmethyl phosphonates with 3-hydroxy-2-(*S*)- α -phenylethyl-3,4-dihydroisoquinolin-1-one (Scheme 12.3). High yields (*ca.* 80%) of the 3-alkylated products are obtained with *ca.* 40% de of the 2(*S*)-3(*R*)-diastereoisomers [11]. Similarly, when ethyl glycine is *N*-protected with (*S*)-menthone, *C*-alkylation under solid:liquid conditions using a non-chiral catalyst (6.4.5) provides a route to chiral α -substituted amino acids with optimum enantiomeric excesses of up to 47% [12].



Scheme 12.3

12.1.1 Reaction of alkylphosphonates with chiral 2-substituted 3-hydroxy-3,4-dihydroisoquinolin-1-one

3-Hydroxy-2-(*S*)- α -phenylethyl-3,4-dihydroisoquinolin-1-one (0.4 g, 1.5 mmol) is stirred at 20–25 °C with (EtO)₂P(O)CH₂CN or (EtO)₂P(O)CH₂CO₂Me (1.8 mmol) in CH₂Cl₂ (30 ml) and TBA-Br (0.1 g, 0.3 mmol) in aqueous NaOH (50%, 2.4 ml) for *ca.* 25 min. The organic phase is separated, washed well with H₂O, dried (Na₂SO₄), and evaporated to yield the 3-alkylated product.

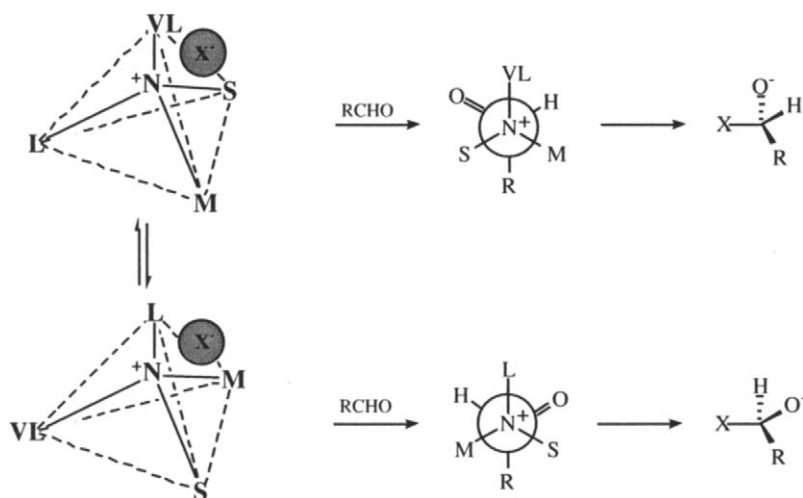
Specific control of the stereochemistry of the chemical reaction is better achieved using chiral phase-transfer catalysts. These catalysts interact specifically with the substrate and sterically hinder the approach of nucleophile to one face of the reactive site. Experimental procedures are essentially the same as those employed in reactions using achiral catalysts where there is no stereochemical control and, in subsequent sections, reference is made back to the appropriate Chapter unless variations in the procedure differ significantly.

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12.2 CHIRAL QUATERNARY AMMONIUM CATALYSTS

An important aspect of stereochemical control is the utilization of chiral reagents to induce asymmetry during a synthetic reaction sequence. In principle, an ammonium salt possessing a chiral nitrogen atom would be the simplest system capable of asymmetric induction. Thus, any ammonium cation possessing four groups with different steric requirements (VL > L > M > S) could form ion-pairs by the interaction of the anion with any one of the four faces of the tetrahedral ammonium ion [1]. Although it might be expected that the most stable ion-pair would be formed by interaction of the anion with the least sterically hindered face and that asymmetric induction in the subsequent reaction would be controlled by the spatial interaction of the ion-pair with the reactive substrate, as shown in Scheme 12.4, in practice the anion is free to change its association with any of the four faces of the ammonium ion. The associa-



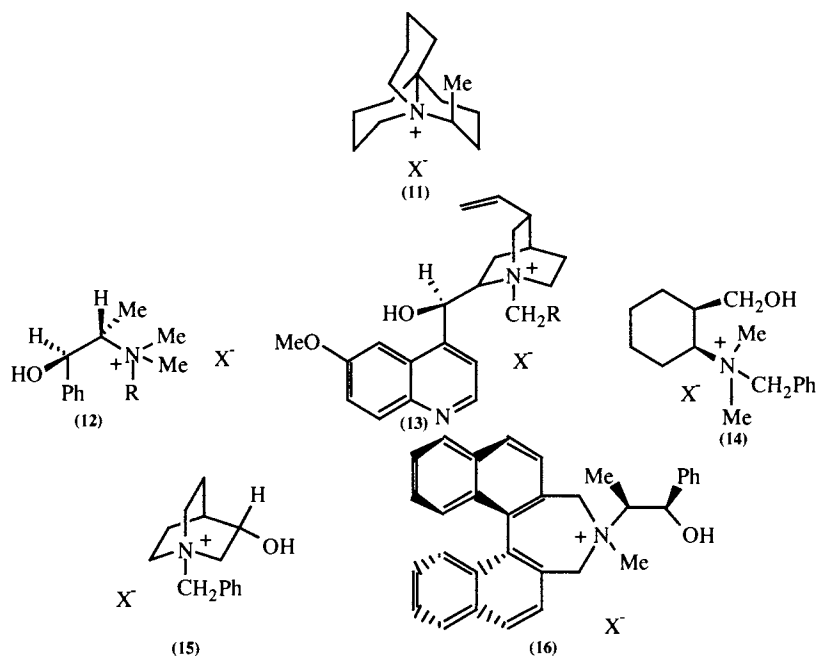
Scheme 12.4

tion constants for the different ion-pairs formed between an anion and the simple chiral tetra-alkylammonium cations are not sufficiently different to result in any significant enantiomeric excess in subsequent reaction. Consequently, the use of such chiral catalysts for asymmetric induction is impractical. For example, even the configurationally and conformationally rigid chiral 2-methylazoniaproellane salts (**11**) do not produce any asymmetric induction in simple *C*-alkylation or Michael addition reactions [2, 3].

In an alternative approach, the chirality of the ammonium catalyst can reside within one of the substituents attached to the nitrogen atom. The majority of the reported examples of successful asymmetric induction result from the use of a quaternary ammonium cation, which possesses chirality at both the nitrogen atom and within a substituent and/or some functionality on the chiral alkyl group. Catalysts having only a non-functionalized chiral *N*-substituent are non-effective [e.g. 4]. The most frequently used chiral catalysts are quaternized derivatives of ephedrine, e.g. (**12**), or of cinchona alkaloids, e.g. (**13**, *R* = Ph) (Scheme 12.5). More sterically demanding and more rigid salts (e.g. **13**, *R* = 10-anthracenyl) are generally more effective stereoselective catalysts [5], although the ephedrinium-type salts (**14**), derived from the (+) and (–) forms *N*-benzyl-*N*-[*cis*-(2-hydroxymethyl)cyclohexyl]methylamine have been found to be no more effective than the simple ephedrinium salts [6, 7]. The electronic character of the *N*-substituents plays an important role. Thus, *N*-(*p*-trifluoromethylbenzyl)cinchoninium salts have greater stereoselective power than the corresponding benzyl salts [e.g. 8–16].

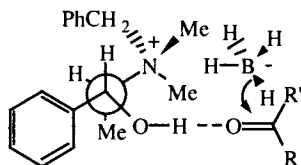
Other chiral catalysts, which have been used with some degree of success include the quinuclidinium salt (**15**) [17] and the ephedrinium derivative (**16**) [18].

The efficiency of the stereochemical control will be governed by the spatial arrangement of the ion-pair and the reactive substrate or, more precisely, the control



Scheme 12.5

is exerted on the stereoselective delivery of the anion from the ion-pair to the reactive site of the substrate. The asymmetric induction is enhanced when the substrate interacts with the ion-pair such that its position with respect to the reactive anion is restrained. Many of the phase-transfer catalysed syntheses in which a high degree of asymmetric induction has been achieved involve nucleophilic reactions with a substrate in which a carbonyl group is either the reactive site, or is in close proximity to the reactive site. In these reactions the success of the ephedrinium or quininium salts results from their ability to form a hydrogen bond between the β -hydroxyethyl groups and the carbonyl group as, for example, in the hydride reduction of a ketone (Scheme 12.6). The importance of H-bonding is illustrated by the complete absence of stereochemical control in the absence of the β -hydroxyethyl substituent, or if the β -hydroxy group is esterified [19, 20]. It is also significant that optimum asymmetric induction is to be found only with the β -hydroxyethylammonium salts, and is negligible with γ - and δ -hydroxyethylammonium cations [21] (Table 12.3). The impor-



Scheme 12.6

TABLE 12.3

Catalytic effect of *N*-methyl ephedrinium and related salts on the borohydride reduction of 3,3-dimethyl-1-phenyl-1-propan-1-one

Catalyst	% overall conversion	Enantiomeric excess
(12)(R = C ₁₂ H ₂₅)	77	13.7
[PhCH(OH)CH ₂ CH ₂ N(C ₁₂ H ₂₅)Me ₃] ⁺ Br ⁻	86	1.1
(-)(<i>R</i>)-[PhCH ₂ CH(Me)N(C ₁₂ H ₂₅)Me ₃] ⁺ Br ⁻	75	0

tance of the β -hydroxyl group is widely accepted, but it has also been proposed that coulombic interactions between the catalyst and substrate are possibly more important [22] and that in alkylation reactions, at least, the hydroxyl group may be initially alkylated [23]. It has also been noted that high enantioselectivity can be achieved for the epoxidation of α,β -unsaturated ketones by hypochlorite using *O*-benzyl-quininium salts [5].

The overall steric demands of the catalyst and the substrate are important in the spatial arrangement of the H-bonded complex. Consequently, although the less rigid ephedrinium salts have been used with some success, they are generally less effective than the derivatives of the cinchona alkaloids, the rigidity of which imposes a greater stereochemical restraint on the structure of the H-bonded complexes.

The significance of the steric factors is demonstrated in, for example, the catalysed Michael addition of the thiophenoxide ion to cyclohex-2-en-1-one, where quininium and cinchonidium salts having the same configurations at C-8(*S*) and C-9(*R*) lead to the same chiral Michael adduct, whereas quinidinium and cinchonium salts having 8(*R*)- and 9(*S*)-configurations produce an adduct of the opposite configuration (Section 12.3). Similarly, although possessing the required β -hydroxyethylamino group, the sterically less demanding *N*-benzyl-*N,N*-dimethyl(1-hydroxy-4-methylthiobut-2-yl)ammonium salts, derived from L-(+)-methionine, are totally ineffective for asymmetric induction reactions [24].

Predictably, the association between the ion-pair and the substrate is influenced by the choice of the organic phase and by the reaction temperature. Polar solvents will not only affect the interaction between the catalysts and substrate, they will also reduce the association of the ion-pair with a resultant increase in 'free' anion over which there is no stereochemical control (Table 12.4).

TABLE 12.4

Effect of solvent upon the phase-transfer catalysed epoxidation of chalcones

Solvent	Dielectric constant	Enantiomeric excess
PhNO ₂	34.80	10%
CH ₂ Cl ₂	9.10	25%
PhCl	5.71	34%
PhMe	2.44	48%
PhH	2.28	54%

The enantiomeric excess resulting from any asymmetric reaction depends on the difference in the activation energies ($\Delta\Delta G$) for the two asymmetric pathways, such that

$$\Delta\Delta G/RT = \ln[(100 + P)/(100 - P)]$$

where P is the enantiomeric excess, i.e. $100[(R - S)/(R + S)]$.

For example, an energy difference of *ca.* 30 kJ mol⁻¹ produces an enantiomeric excess of 50% (i.e. R:S = 3 : 1) at 25 °C, whereas an enantiomeric excess of 90% (i.e. R:S = 19 : 1), 95% (R:S = 39 : 1) and 99% (R:S = 199 : 1) require energy differences of *ca.* 80, 100 and 145 kJ mol⁻¹, respectively. If one accepts the (false) assumption that the stabilities of the ion-pair:substrate complexes would be unaffected by the change in reaction temperature, then an enantiomeric excess of 90% (R:S 19 : 1) at 25 °C resulting from an activation energy difference of 80 kJ mol⁻¹ is reduced to *ca.* 87.5% (R:S = *ca.* 15 : 1), when the reaction temperature is raised to 50 °C. However, as the stabilities of the ion-pairs and the ion-pair:substrate are also reduced at the higher temperature, the effective induced asymmetry will be even further reduced. The optimum stereoselectivity is consequently attained at the lowest operational temperature that is feasible for the reaction.

Thus the highest stereoselectivity is likely to be obtained with short reaction times; low temperatures; high concentrations of the chiral catalyst; non-polar solvents [25].

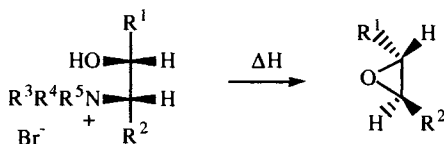
In all work involving chiral catalysts, care has to be taken in the interpretation of the results. The catalyst may be carried over during work-up to give spurious optical rotations but, more significantly, the catalyst may be degraded to yield material which has a high optical activity. For example, hydroxyethylammonium salts produce oxiranes possessing high optical rotations (Scheme 12.7) under strongly basic reaction conditions (Table 12.5) [26, 27].

Many chiral catalysts are commercially available, but others are readily prepared by quaternization of the appropriate chiral base. The preparation of a selection of the more commonly used, or potentially interesting, chiral ammonium salts is presented in 12.1.1.

TABLE 12.5

Stability of ephedrinium and quininium salts under phase-transfer catalytic conditions

Catalyst	Reaction conditions			% decomposition
<i>N</i> -Benzyl- <i>N</i> -methylephedrinium chloride				
	10% aq NaOH	20 °C	15 h	10
	30% aq NaOH	20 °C	10 h	25
	50% aq NaOH	20 °C	10 h	65
<i>N</i> -Benzylquininium chloride				
	30% H ₂ O ₂ /2M NaOH	50 °C	5 h	40
	10% aq NaOH	50 °C	1.5 h	70
	30% aq NaOH	50 °C	1 h	85
	50% aq NaOH	50 °C	0.75 h	80
	aq. KCN	80 °C	24 h	25



Scheme 12.7

12.2.1 General procedures for the preparation of typical chiral quaternary ammonium salts

Method A: Equimolar amounts of the amine and alkyl halide in dry acetone are heated under reflux for 5–10 days. The hot solution is filtered and the filtrate cooled. The quaternary ammonium salt, which crystallizes, is collected and recrystallized [e.g. (–)-*N*-benzylquininium chloride, m.p. 183–188 °C (decomp.) [α]_D –230.5 °C (c. 1.479 in H₂O); (+)-*N*-benzylquinidinium chloride, m.p. 180 °C (decomp.) [α]_D +219.9 °C (c. 0.632 in H₂O); (+)-*N*-benzylcinchoninium chloride, m.p. 248 °C (decomp.) [α]_D +164.8 °C (c. 0.716 in H₂O); (–)-*N*-benzylcinchonidinium chloride, m.p. 212–213 °C (decomp.) [α]_D –175.4 °C (ca. 0.5 in H₂O); (–)-*N*-(4-nitrobenzyl)quininium chloride, m.p. 178–180 °C (decomp.) [α]_D +216.8 °C (c. 0.5 in H₂O); (+)-*N*-(4-trifluoromethylbenzyl)cinchoninium bromide, m.p. 250 °C (decomp.) +140 °C (c. 0.5 in EtOH)].

Method B: An equimolar amount of the alkyl halide is added to the amine in dry EtOH or THF and the solution is heated at 80 °C for 15–20 h. The solution is cooled (Et₂O is added when EtOH is used as the solvent) to precipitate the salt [e.g. (–)-*N*-(2-nitrobenzyl)quininium chloride, m.p. 188–190 °C (decomp.) [α]_D –131.6 °C (c. 0.7 in CH₂Cl₂); (–)-*N*-(2-nitrobenzyl)quinidinium chloride, m.p. 178–180 °C (decomp.) [α]_D –216.6 °C (c. 0.5 in EtOH); (–)-*N*-benzyl-*N*-methylephedrinium chloride, m.p. 198–199 °C (decomp.) [α]_D –8.97 °C (c. 2.0 in EtOH); (–)-*N*-benzyl-*N*-methylephedrinium bromide, m.p. 209–211 °C (decomp.) [α]_D –5.3 °C (c. 4.5 in EtOH); (–)-*N*-dodecyl-*N*-methylephedrinium bromide, m.p. 89–92 °C (decomp.) [α]_D –12.5 °C (c. 1.0 in CHCl₃); (–)-*N*-hexadecyl-*N*-methylephedrinium bromide, m.p. 111–113 °C (decomp.) [α]_D –9.1 °C (c. 1.4 in MeOH); (–)-*N,N*-dimethylephedrinium iodide, m.p. 204–205 °C (decomp.) [α]_D –22.2 °C (c. 3.252 in H₂O); (+)-*N,N*-dimethyl-ψ-ephedrinium iodide, m.p. 211–212 °C (decomp.) [α]_D +36.3 °C (c. 3.278 in H₂O); (–)-*N*-(4-trifluoromethylbenzyl)quininium bromide, m.p. 185–187 °C, [α]_D –153.3 °C (c. 0.18 in MeOH).

(*R*)- and (*S*)-2,2-bis(bromomethyl)-1,1-binaphthyl react with 1(*R*)2(*S*)-ephedrine to give, respectively, the 1(*R*)2(*S*)(*R*)- [m.p. 210–213 °C [α]_D –206 °C (c. 0.6 in pyridine)] and 1(*R*)2(*S*)(*S*)-ephedrinium salts [m.p. 253–254 °C [α]_D +343 °C (c. 0.6 in pyridine)].

Method C: As an alternative to Method B, an equimolar amount of the alkyl halide is added to the amine in dry PhMe and the solution is heated under reflux for 12 h. The solution is cooled and the insoluble salt is collected.

Method D: MeBr is bubbled through a methanolic solution of the base for ca. 8 h at 0 °C. The solvent is evaporated and the salt recrystallized from EtOH:Et₂O [e.g. (+) and (–) forms of *N*-benzyl-*N*-[*cis*-(2-hydroxymethyl)cyclohexyl]methylamine give (+)-[m.p. 175–176 °C, [α]_D +34.6 °C (c. 1.04 in CHCl₃)] and (–)-[m.p. 176–177 °C, [α]_D –34.6 °C (ca. 1.00 in CHCl₃)] *N*-benzyl-*N*-[*cis*-(2-hydroxymethyl)cyclohexyl]dimethylammonium bromide, respectively].

Method E: (–)-*N*-methylquininium iodide, (+)-*N*-methylquinidinium iodide, (–)-*N*-methylcinchonidinium iodide, and (+)-*N*-methylcinchoninium iodide, prepared by

Method B, are suspended in H₂O and shaken with freshly prepared silver chloride (or IRA-410(Cl) ion exchange resin) to yield (–)-*N*-methylquinidinium chloride, m.p. 196–198 °C (decomp.) [α]_D –211.7 °C (c. 0.655 in H₂O) and (+)-*N*-methylquinidinium chloride, m.p. 250–251 °C (decomp.) [α]_D +253.1 °C (c. 1.505 in H₂O), (–)-*N*-methylcinchonidinium chloride, m.p. 232–233 °C (decomp.) [α]_D –142.7 °C (c. 1.489 in H₂O), and (+)-*N*-methylcinchoninium chloride m.p. 270 °C (decomp.) [α]_D +225.1 (c. 1.482 in H₂O), respectively.

Method F: *N*-Benzylcinchoninium hydroxide, prepared from the bromide salt (0.46 g, 1 mmol) using **12.2.2**, in MeOH (20 ml) is neutralized to pH 7 with aqueous HF (1M). The solution is evaporated and the residue is taken up in PhH:MeCN (1 : 1, 10 ml). The solvent is removed and the procedure is repeated to yield the fluoride salt, which is dried over P₂O₅ at 40 °C.

12.2.2 Quininium and quinidinium hydroxides

Amberlite IRA-410 (10 g) is fully converted into its hydroxide form by treatment with aqueous NaOH (ca. 4%, 250 ml) and the resin is then washed with H₂O (250 ml) and EtOH (250 ml). Addition of the (–)-*N*-methylquininium and (+)-*N*-methylquinidinium iodides (ca. 2.0 mmol) in EtOH to a column of the resin and elution with EtOH gives the respective hydroxides.

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12.3 CARBON-CARBON BOND FORMATION

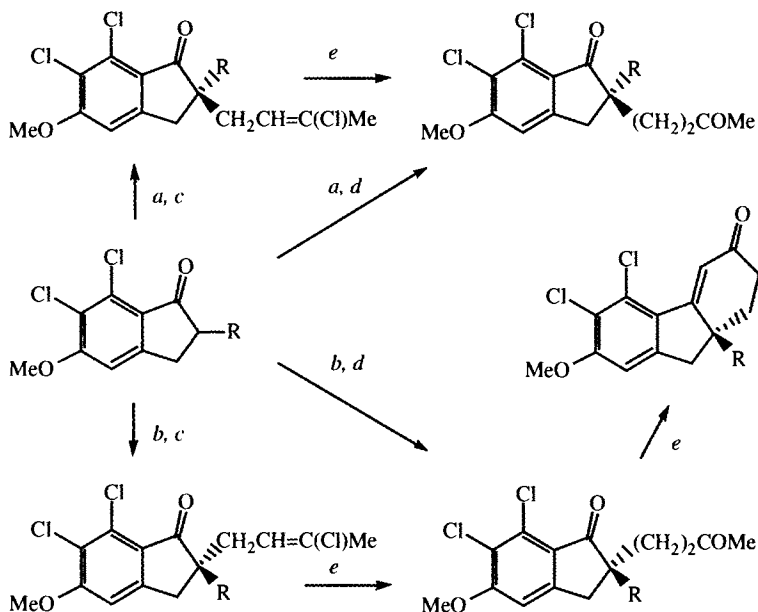
Alkylation reactions

Early studies of the stereospecific alkylation of activated methylene groups under phase-transfer conditions using *N*-methylephedrinium salts [1, 2] were not particularly impressive and the claimed asymmetric induction has been challenged on the grounds of carry over of the catalysts or degraded catalysts with the products [3]. However, it has been shown later that reliable high induction (>90% ee) can be achieved in the stereospecific *C*-alkylation of benzylic ketones using *N*-(4-trifluoromethylbenzyl)cinchonidium and cinchonium bromides [4–7] using a procedure analogous to 6.2.2. The high activity of these catalysts is attributed to the almost coplanarity of the quinoline and *N*-benzyl rings of the catalysts, which can associate via π - π interaction respectively with, for example, the substituted benzene and phenyl rings of enolate anion of 6,7-dichloro-5-methoxy-2-phenylindanone [6, 7] thereby protecting one face and presenting an unhindered face of the enolate anion to the alkylating agent. Alkylation of the indanone with 1,3-dichlorobut-2-ene and subsequent solvolysis of the vinyl chloride [5] produces the same product as that obtained by a Michael reaction with methyl vinyl ketone (Scheme 12.8). Depending on whether the catalyst is used, the (*R*)- and (*S*)-isomers can be obtained.

The stereospecific *C*-alkylation of a range of benzylic ketones, such as tetralones, 2-phenylcyclohexanones and cycloheptanones, and 2-phenyl- γ -lactones, has also been described [8]. For example, *N*-(4-trifluoromethylbenzyl)cinchonidium bromide catalyses the reaction of 1,5-dibromopentane with 7-methoxy-1-methyl-2-tetralone to yield the (*R*)-1-(5-bromopentyl) derivative (75% yield with 60% ee).

Catalysis of the *C*-alkylation of 5-methoxy-1,3-dimethyloxindole with chloroacetonitrile by *N*-(3,4-dichlorobenzyl)cinchoninium or quininium chloride leads in good yield to the (*S*)-3-alkylated derivative (78% ee), which provides an efficient stereospecific route to the anticholinesterase agent, (–)-physostigmine [9]. Other analogous alkylation reactions have been reported [10].

Alkylation of the Schiff's bases derived from glycine esters and benzaldehyde or benzophenone (*cf.* Section 6.2) in the presence of chiral phase-transfer catalysts leading to stereospecific formation of chiral α -amino acids [11, 12]. Synthetic procedures (6.2.27B and C) using (–)-*N*-benzylcinchonidium chloride have been reported to yield optical purities >90%, but these results have not been reproduced in other laboratories [13]. Using *N*-(4-trifluoromethylbenzyl)cinchonium and cinchonidium bromides, a high overall conversion (>80%) has been achieved with a range of



a *N*-(4-trifluoromethylbenzyl)cinchonidinium bromide. *b* *N*-(4-trifluoromethylbenzyl)cinchoninium bromide.
c $\text{ClCH}_2\text{CH}=\text{C}(\text{Cl})\text{Me}$. *d* $\text{MeCOCH}=\text{CH}_2$. *e* H_2SO_4

Scheme 12.8

alkylating agents, but with enantiomeric excesses of the chiral amino acids of only 40–60% [13–15]. A higher degree of asymmetric induction was observed with *t*-butyl esters, compared with the ethyl esters, and solid:liquid catalytic conditions using potassium hydroxide:potassium carbonate gave higher induction than liquid:liquid conditions. A theoretical study of the mode of action of the chiral catalyst [16] has suggested, contrary to widespread belief, that the presence of the β -hydroxy group is not critical in the stereochemical control of the alkylation reactions and that coulombic forces are important in the complexed species. It is also conceivable that the hydroxyl group of the catalyst is alkylated in the initial steps of the reaction [17].

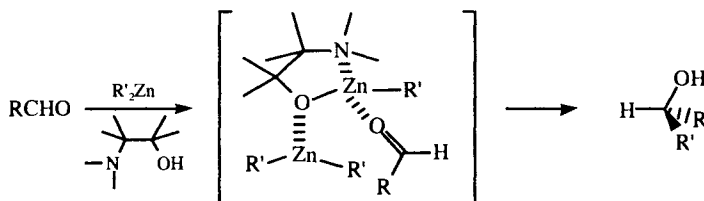
(2*S*)-1-Methyl-1-(*N*-diphenylmethyleamino)-2-hydroxymethylpyrrolidinium salts catalyse *C*-alkylation of *N*-benzylimines leading to chiral secondary amines in high yield (>70%) and high stereoselectivity (>90% ee) [18].

Asymmetric alkylation of α -substituted benzyl cyanides has been achieved using *N*-benzylquininium and cinchonium salts using procedures analogous to those described in 6.2.2 [19, 20]. Analogous reactions catalysed by 1-alkyl-3-hydroxyquinuclidinium salts are less effective than those catalysed by quininium salts [20], whereas 1-methyl-1-diphenylmethyleimino-2(*S*)-hydroxymethylpyrrolidinium iodide is a more effective catalyst (>70% ee) [18].

Carbanionic attack on carbonyl groups

Attempts to produce chiral cyanhydrins under phase-transfer catalytic conditions (3.3.9) using ephedrinium or cinchoninium catalysts has been singularly unsuccessful [21, 22]. Optical purities varying from 0 to 60% have been recorded [22], but verification of the reproducibility of the higher values is needed. Similarly, nucleophilic attack on a carbonyl group by the trichloromethyl anion under phase-transfer catalytic conditions (see Section 7.4) in the presence of benzylquininium chloride produces a chiral product, but only with an enantiomeric excess of 5.7% [23]. The veracity of this observation has also been questioned [24].

In contrast, the stereospecific *C*-alkylation of carbonyl groups with dialkylzinc compounds, catalysed by chiral alkaloids, is well investigated and produces chiral alcohols [e.g. 25–31]. As with the reaction using non-chiral catalysts [32], the reaction rate is enhanced by the phase-transfer catalyst and the competing reduction reaction is suppressed. The precise mechanism by which asymmetry is induced by chiral β -hydroxyamines is not known, but it is assumed that an intermediate complex of the type shown in Scheme 12.9 is involved [33–35]. β -Hydroxyalkylpyridines and bipyridyls have also been used with some success as catalysts [36]. Asymmetric induction is generally lower when polymer-supported or silica-bound catalysts are used instead of the ‘free’ alkaloid [e.g. 37–39]. However, when the chiral β -hydroxy-amino group is well separated from the polymeric backbone by a spacer, the overall yield and asymmetric induction is comparable with the ‘free’ catalyst [40]. The corresponding reactions catalysed by the salts of the chiral alkaloids have also been reported [41]. Although the intermediate complex does not have the interaction between the nitrogen atom and the zinc atom, there is obviously sufficient rigidity within the system to induce asymmetry in the final product. In contrast with the observed effectiveness of the homogeneous catalysis and induction by the free bases, it is noteworthy that the asymmetric induction with the chiral ammonium salts is more effective when the catalyst is not soluble in the organic phase [41] (Table 12.6).



Scheme 12.9

12.3.1 Chiral addition of dialkylzincs to aldehydes

Method A (catalysed by chiral β -hydroxyamines): The chiral catalyst (0.6 mmol) and the aldehyde (1 mmol) in $n\text{-C}_6\text{H}_{14}$ (2 ml) are stirred at room temperature for 20 min. The mixture is cooled to 0°C , the dialkylzinc (1M in $n\text{-C}_6\text{H}_{14}$, 2.2 ml) is added dropwise, and

TABLE 12.6

Effect of the catalyst upon the chiral reaction of benzaldehyde with diethylzinc

Catalyst	Solvent	% overall yield	% ee
Free base ^a	<i>n</i> -C ₆ H ₁₄ ^b	100	90
Silica-bound ^a	<i>n</i> -C ₆ H ₁₄ ^c	81	43
Polymer-supported ^d	<i>n</i> -C ₆ H ₁₄ ^c	83	89 ^e
Polymer-supported ^f	<i>n</i> -C ₆ H ₁₄ ^c	91	82
Salt ^g	<i>n</i> -C ₆ H ₁₄ ^c	90	74
Salt ^g	PhH: <i>n</i> -C ₆ H ₁₄ ^c	76	73
Salt ^g	DMF: <i>n</i> -C ₆ H ₁₄ ^b	71	0

^a *N*-Methylephedrine. ^b Homogeneous system. ^c Heterogeneous system. ^d Polystyrene-supported *N*-methylephedrine. ^e 33% ee with dimethylzinc. ^f Supported *N*-butyl-ephedrine separated from the polystyrene-backbone by a CH₂Q(CH₂)₆ link. ^g *N*-benzyl-*N*-methylephedrinium chloride.

the mixture is stirred at 0°C for *ca.* 16 h. Aqueous HCl (1M, 5 ml) is added and the organic phase is separated. The aqueous phase is extracted with CH₂Cl₂ (4 × 7 ml) and the combined organic solutions are dried (Na₂SO₄), and evaporated to yield the chiral secondary alcohol.

Method B (catalysed by polymer-supported chiral β-hydroxyamines): The aldehyde (1 mmol) is added to the polymer-supported catalyst (0.298 g) in *n*-C₆H₁₄ (2 ml) at 0°C and the mixture is stirred for 15 min. The dialkylzinc (1M in *n*-C₆H₁₄, 2.2 ml) is added and the mixture is stirred for 1–8 days at 0°C. The reaction is quenched with aqueous HCl (1M, 5 ml) and the mixture is filtered and extracted with CH₂Cl₂ (3 × 10 ml). The dried (Na₂SO₄) extracts are evaporated to yield the chiral secondary alcohol.

Method C (catalysed by chiral β-hydroxyammonium salts): The chiral ammonium salt (0.6 mmol) and the aldehyde (1 mmol) in the appropriate solvent (2 ml) are stirred at room temperature for 20 min. The dialkylzinc (1M in *n*-C₆H₁₄, 2.2 ml) is added dropwise, and the mixture is stirred at room temperature for 3–6 days. The chiral alcohol is isolated using the procedure described in 12.3.1.A.

In a similar fashion to its reaction with the aldehydes, diethylzinc reacts with (*N*-diphenylphosphonyl)imines in the presence of chiral alkaloids to produce, after hydrolysis, chiral 2-substituted propylamines [42].

Aldol condensation of silyl enol ethers with aldehydes (6.3.3) in the presence of *N*-benzylcinchonium fluoride proceeds in high yield and high stereoselectivity [43], whereas nucleophilic trifluoromethylation of aldehydes and ketones to yield chiral alcohols has been achieved at low temperature using trifluoromethyltrimethylsilane in the presence of *N*-(4-trifluoromethylbenzyl)cinchonium fluoride [44]. An analogous reaction of aldehydes with *O*-silyl ketene acetals derived from *t*-butyl glycinate imines under the influence of *N*-(9-anthracenylmethyl)-*O*-benzylcinchonidinium hydrogen difluoride provides an enantioselective synthesis of β-hydroxy-α-amino esters [45].

12.3.2 β-Hydroxy-α-aminoacetic esters

The aldehyde (3.38 mmol) and the cinchonidinium catalyst (40 mg, 16.9 μmol) in CH₂Cl₂ (0.8 ml) are added to the *O*-silyl ketene acetal (0.676 mmol), derived from

$\text{Ph}_2\text{CH}=\text{NCH}_2\text{CO}_2t\text{-Bu}$, in CH_2Cl_2 (4 ml) and $n\text{-C}_6\text{H}_{14}$ (14.4 ml) at -78°C under N_2 . The mixture is stirred at -78°C for 7 h and the reaction is then quenched by the addition of aqueous NH_4Cl and Et_2O . The ethereal phase is separated, washed well with H_2O and brine, dried (MgSO_4), and evaporated. The residue is taken up in THF (8 ml) and aqueous citric acid (0.5M, 5 ml) and the mixture is stirred at room temperature for 15 h. The THF is removed at 20°C under vacuum and the aqueous mixture is washed with Et_2O , neutralized with NaHCO_3 , and saturated with NaCl . The mixture is extracted with CH_2Cl_2 (3×15 ml) and the dried (MgSO_4) extracts are evaporated to yield the β -hydroxy- α -aminoacetate.

The cycloaddition of aldehydes and ketones with ketene under the influence of quinine or quinidine produce chiral 2-oxetanones [46, 47]. Solvolytic cleavage of the oxetanone, derived from chloral, and further solvolysis of the trichloromethyl group leads to (*S*)- and (*R*)-malic acids with a 98% ee [46] (the chirality of the product depends on the configuration of the catalyst at C-8 and, unlike other alkaloid-induced reactions, it is apparently independent of the presence of the hydroxyl group). No attempts have been made to catalyse the reaction with chiral ammonium salts.

A stereoselective tandem iodination and aldol-type condensation has been described for the reaction of methyl propiolate and carbonyl compounds in the presence of a stoichiometric amount of tetra-*n*-butylammonium iodide and zirconium chloride to yield Z-3-iodo-2-(1-hydroxyalkyl)propenoates, as the major products [48]. No reaction occurs in the absence of the Lewis acid. There does not appear to be any control on the chirality of the hydroxyl centre.

12.3.3 Tandem addition-aldol reaction with methyl propiolate

ZrCl_2 (0.28 g) is added to $\text{HC}\equiv\text{CCO}_2\text{Me}$ (84 mg, 1 mmol), the carbonyl compound (1.2 mmol) and TBA-I (0.4 g, 1.1 mmol) in CH_2Cl_2 (5 ml) with stirring at 0°C . When the reaction is complete, as shown by TLC analysis, H_2O (5 ml) is added and the mixture is extracted with CH_2Cl_2 (3×5 ml). The dried (MgSO_4) extracts are evaporated to yield the iodopropenol.

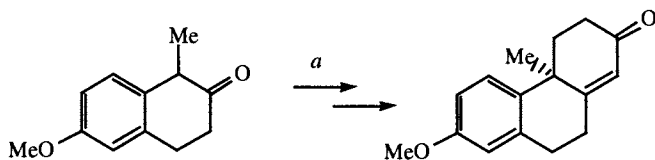
The catalysed reaction of aryl aldehydes with ammonia and chloroform (7.4.3) in the presence of chiral ephedrinium salts leads to the asymmetrically induced formation of α -amino acids. Yields are variable and with *ca.* 20–30% ee [49].

Michael reactions (see Section 6.4)

Poor stereoselectivity (<30% ee) is recorded for the Michael addition of 1,3-diketones with nitroalkenes using cinchona bases [50] and early work recorded <25% ee using *N*-methylquininium and quinidinium hydroxides [51, 52]. In contrast, indanones have been reported to react with methyl vinyl ketone in the presence of a cinchoninium salts to produce a chiral (*S*)-product in >95% yield (80% ee) [7]. Surprisingly, the (*R*)-isomer is obtained less readily (ee 40–60%) using cinchonidinium salts. Both isomers are obtained in high optical purity (>80% ee) via alkylation with 1,3-dichlorobut-2-ene and subsequent ring closure yields the Robinson

annulation product (Scheme 12.8). Analogous reactions, catalysed by polymer-supported cinchona alkaloids produce high chemical yield, but poor optical induction [53]. Comparison of liquid:liquid and solvent-free phase-transfer catalytic conditions has shown that, although the solvent-free conditions lead to higher overall yields, liquid:liquid conditions are better for enantioselective reactions using cinchoninium catalysts [54].

The Robinson annulation reaction of 7-methoxy-1-methyl-2-tetralone with methyl vinyl ketone in the presence of *N*-(4-trifluoromethylbenzyl)cinchonidinium bromide produces the *S*-isomer of the tricyclic compound (Scheme 12.10) with an 81% conversion (81% ee) [8].



a MeCOCH=CH_2 , 60% aq. KOH, PhMe, *N*-(4-trifluoromethylbenzyl)cinchonidinium bromide

Scheme 12.10

Michael addition of nitromethane to chalcones [55, 56], and of nitroethane to vinyldisulphoximides [57], in the presence of *N*-benzylquininium salts proceeds in high yield, but with low stereoselectivity (~10% ee). These observations should be compared with the conflicting results reported for similar reactions: (a) when catalysed by quinidine providing a 60% enantiomeric excess of the chiral product with a 100% overall conversion [58] and (b) the total failure of quinine to catalyse the reaction [51, 55], while catalysing the analogous reaction of methylsulphones with but-3-en-2-one [56, 59]. *N*-Dodecyl-*N*-methylphedrinium fluoride is reported to be a more effective catalyst than the quininium salt (24–26% ee) in the reactions of nitromethane and the methylsulphones with the electron-deficient alkenes, but the overall conversions are only *ca.* 50% [55, 56, 60].

The regio- and diastereo-selectivity of the Michael addition of 2-phenylcyclohexanone with α,β -unsaturated ketones are dependent on the reaction conditions. Mixtures of all six diastereoisomers resulting from reaction at either the 2- or 6-position of the cyclohexanone ring can be obtained using solid potassium hydroxide with tetra-*n*-butylammonium or *N*-benzylephedrinium bromide catalysts. At 20°C with tetra-*n*-butylammonium bromide, the ratio of the 2,2- and 2,6-disubstituted cyclohexanones is *ca.* 3:2, but at higher temperatures with solid potassium *t*-butoxide the kinetically formed 2,6-isomer predominates (*ca.* 5:1) with the (2*S*,6*R*,1*R'*)-stereoisomer dominant, whereas greater amounts of the thermodynamically preferred 2,2-(2*S*,1*R'*)-isomer are obtained with the chiral catalyst [61].

The stereoselective Michael addition of the anion derived from diethyl acetylaminomalonate with chalcone has been found to be most effective under solid:liquid two-phase conditions in the absence of an added solvent [62]. For optimum overall conversion and enantiomeric excess (56% with 60% ee), *N*-benzyl-*N*-methyl-

ephedrinium bromide was shown to be more effective than quininium and related salts. In toluene, the yield was only 51% with 28% ee.

Diastereomeric excesses of up to 56% have been claimed for the preparation of α -amino- β -hydroxy acids via the aldol condensation of aldehydes with *t*-butyl *N*-(diphenylmethylene)glycinate [63]. It might be expected that there would be thermodynamic control of the C–C bond formation influenced by the steric requirements of the substituents, but the use of cinchoninium and cinchonidinium salts lead to essentially the same diastereoselectivity. The failure of both tetra-*n*-butylammonium and benzyltriethylammonium chloride to catalyse the reaction is curious.

12.3.4 Diastereoselective preparation of α -amino- β -hydroxy acids

Aqueous NaOH (5% 270 μ l), followed by the aldehyde (0.85 mmol), are added at room temperature under argon to a stirred mixture of $\text{Ph}_2\text{CH}=\text{NCH}_2\text{CO}_2t\text{-Bu}$ (0.05 g, 0.17 mmol) and *N*-benzylcinchoninium chloride (7.1 mg, 0.017 mmol) in CH_2Cl_2 (1.7 ml). The mixture is stirred at room temperature for 3–4 h until the reaction is complete, as shown by TLC. H_2O (10 ml) and CH_2Cl_2 (10 ml) are added and the organic phase is separated and evaporated. The residue is taken up in Et_2O , washed well with H_2O and brine, dried (MgSO_4), and evaporated. The crude product is purified by chromatography from silica to yield the diastereomeric mixture.

Asymmetric induction has been noted [64] when ethyl glycine, protected as its imine by (*S*)-menthone, is allowed to react with ethyl acrylate under phase-transfer catalytic conditions using tetra-*n*-butylammonium bromide. An overall yield of 43% was achieved with 46% ee. The stereoselectivity of the reaction was not enhanced when *N*-benzylquininium or cinchoninium chloride were used and, unlike reactions catalysed by chiral catalysts, the enantiomeric excess increased, when a more polar solvent was used.

12.3.5 Chiral α -amino acids from imines derived from (*S*)-menthone

Ethyl acrylate (0.52 g, 5.2 mmol) in dry MeCN (5 ml) is added to powdered $\text{K}_2\text{CO}_3\text{:NaOH}$ (5:1, 1.2 g), TBA-Br (0.16 g, 0.5 mmol) and the ketoimine (1.27 g, 5 mmol) in MeCN (20 ml). The suspension is stirred at 0°C for 1 h and then filtered. The solid is washed with MeCN (10 ml) and the combined MeCN solutions are evaporated. The residue is extracted with Et_2O (2 \times 25 ml) and the extracts are washed well with H_2O , dried (MgSO_4), concentrated, and subjected to chromatography from silica to yield the chiral imine.

Carbene reactions

Dichlorocarbene, produced under basic conditions from chloroform (7.1.1) reacts with *cis,trans,trans*-cyclododeca-1,5,9-triene to produce the mono-, bis- and tris-insertion adducts, depending on the reaction conditions and the catalyst used [65, 67]. Early claims that the carbene is activated by the hydroxyethylammonium

catalyst to attack a *trans* C=C bond preferentially [65] has been disproved [66], as has the claim [67] that the catalytic effect of tertiary amines or ephedrinium salts induces asymmetry in the products [24, 68].

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12.4 CARBON–NITROGEN, CARBON–OXYGEN, CARBON–SULPHUR ETC

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12.4 CARBON–NITROGEN, CARBON–OXYGEN, CARBON–SULPHUR AND CARBON–HALOGEN BOND FORMATION

Solid:liquid phase-transfer catalysed *N*-alkylation of potassium phthalimide (**5.2.10**) with racemic α -bromopropionic esters, catalysed by cinchoninium and cinchonidinium salts, selectively produces one of the stereoisomers [1–3] (Table 12.7). Optimum optical purity is achieved using dioxane or tetrahydrofuran as solvents. Although both the cinchonidinium and cinchonium salts catalysed alkylation with optically pure (*S*)(–)-ethyl 2-bromopropionate, higher optical purity of the product was achieved with the cinchonium catalyst. The corresponding displacement of the halogen stereoselectively from the racemic α -bromopropionate with oxygen or sulphur nucleophiles has met with less success [2]. Overall conversion and optical purity of the products are generally low.

The stereochemical control of the Gabriel reaction by chiral catalysts can be further enhanced in the synthesis of optically active α -amino acids when optically pure (–)-bornyl α -bromo esters are used (Table 12.8) [4].

Stereoselective aziridation of electron-deficient alkenes by *N*-acyl arylhydroxylamines (Scheme 12.11) is facilitated by cinchonium salts [5]. Optimum selectivity

TABLE 12.7

Selective *N*-alkylation of potassium phthalimide by ethyl α -bromopropionate^a

Alkylating agent	Catalyst ^b	Solvent	Major isomer	Optical purity ^c
(±) MeCHBrCO ₂ Et	A	MeCN	R/S	0
	A	AcOEt	S	7.7
	A	dioxan	S	12.1
	A	THF	S	9.5
	B	THF	R	19.1
(S)(-) MeCHBrCO ₂ Et	A	THF	R	11.6
	B	THF	R	52.3

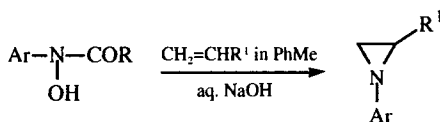
^a 20 mmol of alkylating agent, 25 mmol potassium phthalimide and 1 mmol of catalyst in 60 ml solvent at reflux temperature. ^b A: *N*-benzylcinchonidinium chloride; B: *N*-benzylcinchoninium chloride. ^c Optical purity = $[\alpha]_{\text{obs}}/[\alpha]_{\text{max}} \times 100$.

TABLE 12.8

Examples of the effect of double asymmetric induction on the Gabriel synthesis of optically active α -amino acids

Alkylating agent	% ee	
	With TBA-Br	With <i>N</i> -benzylquininium-Cl
MeCHBrCO ₂ Et	0	5.8
EtCHBrCO ₂ Et	0	4.2
MeCHBrCO ₂ (-)-bornyl	12.9	38.3
EtCHBrCO ₂ (-)-bornyl	7.4	20.1

(ee >60%) is achieved in toluene under dilute basic conditions, but in low yield (<15%). Maximum yields are obtained under more strongly basic conditions (~80%), but selectivity drops (ee ~45%). It is significant that cinchonium and cinchonidinium salts produce identical chiral aziridines.



Scheme 12.11

12.4.1 Aziridation of alkenes

The alkene (5 mmol) in PhMe (8 ml) is stirred with the *N*-acyl arylhydroxylamine (0.52 mmol) and the chiral catalyst (0.05 mmol) in aqueous NaOH (33%, 1 ml)* at room temperature for 2.5 h. A further amount (0.05 mmol) of catalyst is added and the mixture stirred for an additional 2 h. The solvent and excess alkene are removed under vacuum and the residue is taken up in Et₂O (15 ml). The extract is washed with H₂O (3 × 20 ml), dried (Na₂SO₄), and evaporated to yield the aziridine. (*Higher ee is achieved using 9% aqueous NaOH.)

12.4 CARBON–NITROGEN, CARBON–OXYGEN, CARBON–SULPHUR ETC

The use of quininium salts can add to the high stereoselectivity (65–80% ee) that can be achieved under phase-transfer catalytic conditions in the synthesis of oxiranes by the Darzens reaction (Section 12.1) from chloromethylsulphones and aromatic aldehydes [6].

12.4.2 Chiral oxiranes

Powdered KOH (113 mg) is added to the aryl aldehyde (0.6 mmol), the chloromethylsulphone (0.5 mmol) and *N*-(4-trifluoromethylbenzyl)quininium bromide (28 mg, 0.05 mmol) in PhMe (3 ml) at room temperature and the mixture is stirred for 2 h. Aqueous HCl (1M, 3 ml) is added to quench the reaction and the mixture is extracted with AcOEt (3 × 15 ml). The extracts are washed with brine (10 ml), dried (Na₂SO₄), and evaporated to yield the chiral oxirane.

Optically pure alcohols are converted via their mesylates into the corresponding chiral haloalkanes with the opposite configuration (>70% with an optical purity ~90%) by a liquid:liquid phase-transfer catalysed S_N² reaction (2.1.5) with the appropriate potassium halide [7]. The preparation of chiral fluorides normally requires more vigorous conditions (160 °C, 14 h in an autoclave). By-products of the reaction are the alcohol and alkene.

Polymer-supported [e.g. 8, 9] and silica-supported [10] cinchona alkaloids have been used in the asymmetric dihydroxylation of alkenes using osmium tetroxide. Enantiomeric excesses >90% have been achieved for diols derived from styrene derivatives.

C-alkylated Meldrum's acid derivatives are cleaved asymmetrically by alkoxide anions in the presence of quininium salts to yield chiral half esters (9.2.2) [11]. Thus, benzylquininium and cinchonidinium salts produce *R*-hemi-esters and the cinchonium and quinidinium salts produce the *S*-hemi-esters from, for example, 2,2,5-trimethyl-5-phenyl-1,3-dioxane-4,6-dione.

Asymmetric induction of the Michael addition of thiols to electron-deficient alkenes (4.6.1) has been achieved in high overall conversion using both 'free' [e.g. 12–20] and polymer-supported [e.g. 21, 22] cinchona alkaloids and their salts [23–25], but with varying degrees of optical purity. The corresponding asymmetric Michael addition of selenophenols to cyclohex-2-enones is promoted by cinchonidine to give a chiral product (43% ee) [26].

Stereoselective kinetic control of the *O*-methylation of racemic mixtures of secondary alcohols has been reported using (*S*)-(+)-(2-methylbutyl)triethylammonium bromide as the catalyst [27]. However, the claim that the (*R*)-(+)-methyl ether (48% ee) is produced from racemic 1-hydroxy-1-phenylethane leaving the (*S*)-alcohol unchanged has been shown to be totally spurious [28].

Stereoselective ring cleavage and monoesterification of chiral Meldrum's acid derivatives has been achieved in high yield with a 34% enantiomeric excess under phase-transfer catalytic conditions in the presence of *N*-benzylquininium chloride [29]. A similar asymmetric ring-opening of prochiral (meso) acid anhydrides with

methanol in the presence of chiral alkaloids produces the optically active half-ester [30]; the use of chiral ammonium salts has not been reported.

12.4.3 Stereoselective cleavage and esterification of Meldrum's acid derivatives

Methanolic MeONa (3M, 0.12 ml) is added to the *N*-benzylquininium or quinidinium chloride (0.162 g, 0.36 mmol) in dry THF (2 ml) at room temperature. The mixture is stirred at room temperature for 10 min and the Meldrum's acid derivative (0.3 mmol) in dry PhMe (13 ml) is added at -50°C . The course of the reaction is monitored by GLC. On completion, the mixture is stirred for a further 15 min at -50°C and aqueous citric acid (3%, 30 ml) is added. The aqueous phase is separated, and extracted with Et_2O (3×20 ml). The combined extracts are washed with brine (20 ml) and dried (Na_2SO_4). Evaporation of the Et_2O under reduced pressure gives the monomethyl malonic ester.

Attempts to control the stereochemistry of the addition of chlorine to alkenes using ephedrinium and cinchoninium salts give only low optical activity [31].

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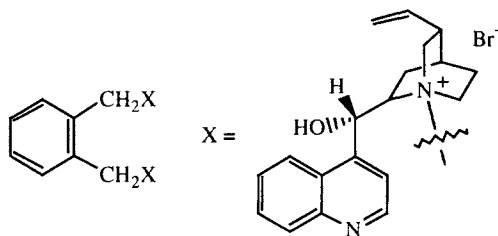
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12.5 OXIDATION REACTIONS

Epoxidation

Direct phase-transfer catalysed epoxidation of electron-deficient alkenes, such as chalcones, cycloalk-2-enones and benzoquinones with hydrogen peroxide or *t*-butyl peroxide under basic conditions (Section 10.7) has been extended by the use of quininium and quinidinium catalysts to produce optically active oxiranes [1–16]; the alkaloid bases are less efficient than their salts as catalysts [e.g. 8]. In addition to *N*-benzylquininium chloride, the binaphthyl ephedrinium salt (**16** in Scheme 12.5) and the bis-cinchonidinium system (Scheme 12.12) have been used [12, 17]. Generally, the more rigid quininium systems are more effective than the ephedrinium salts.



Scheme 12.12

The validity of early results has been questioned [18], but more recent experiments clearly show that high enantiomeric excesses (up to 92%) of the chiral epoxides can be obtained using the quininium catalysts in toluene [4] or dibutyl ether [15]. Effective enantiomeric epoxidation (ee 69–89%) of α,β -unsaturated ketones has also been achieved using sodium hypochlorite catalysed by *N*-anthracenyl-methylquininium and quinidinium salts [19]. It is intriguing that both the quininium salts and their *O*-benzyl derivatives are effective catalysts for the epoxidation reaction with hypochlorite (>85% with ee >80%). Additionally, it is noteworthy that both catalysts are relatively ineffective for the epoxidation of the alkenes with alkaline peroxide (~60% with ee <10%) and that, whereas the quininium salt and peroxide produces oxiranes with the opposite configuration to those obtained using hypochlorite, the same stereoisomers are obtained using peroxide or hypochlorite and the *O*-benzylquininium salts [19]. This contrasts with other reports which claim that *O*-allylquininium salts are ineffective catalysts for epoxidation with hydrogen peroxide [15].

12.5.1 Asymmetric epoxidation of π -deficient alkenes

Method A: The alkene (1 mmol) and the quininium salt* (0.05 mmol) in *n*-Bu₂O (3 ml) and aqueous H₂O₂ (30%, 1 ml) are stirred at 4 °C for 20 min. LiOH (72 mg) is added and the mixture is stirred for a further 37 h at 4 °C. Aqueous HCl (1M, 3 ml) is added and the mixture is extracted with Et₂O (3 × 15 ml) and washed with brine (20 ml). Evaporation of the dried (Na₂SO₄) organic phase yields the chiral oxirane. (*Optimum ee was obtained using the *N*-(4-iodobenzyl) salt.)

Method B: The quininium salt* (0.05 mmol) and LiOH (47.9 mg) are added to the alkene (1 mmol) in CHCl₃ (3 ml) and aqueous H₂O₂ (30%, 1 ml) at -10 °C and the mixture is stirred for *ca.* 5 h at -10 °C. Aqueous HCl (1M, 3 ml) is added and the mixture is extracted with Et₂O (3 × 15 ml) and washed with brine (20 ml). Evaporation of the dried (Na₂SO₄) organic phase yields the chiral oxirane. (*Optimum ee was obtained using the *N*-(α -naphthyl) salt.)

Method C: *t*-BuO₂H in PhMe (80%, 10 ml) is added with stirring at room temperature to the alkene (15 mmol) and *N*-benzylquininium chloride (0.5 g, 1.1 mmol) in PhMe (10 ml). The mixture is stirred for 5 h, Et₂O (25 ml) is added, and the mixture is extracted with H₂O (4 × 50 ml). The dried (MgSO₄) organic phase is evaporated to yield the oxirane.

Method D: Aqueous NaOCl (115 g, 1.2 ml) is added to the alkene (1 mmol) and chiral catalyst (0.1 mmol) in PhMe (10 ml) at 25 °C. The mixture is stirred for 24–48 h and H₂O (5 ml) is then added. The aqueous phase is separated, extracted with EtOAc (10 ml), and the combined organic solutions are dried (Na₂SO₄) and evaporated to yield the chiral oxirane.

The stereoselective epoxidation of chalcones, followed by acid-catalysed ring closure and concomitant cleavage of the epoxide ring, provides a very efficient route to chiral flavon-3-ols and, subsequently, by borohydride reduction to produce flavan-3,4-diols [13, 14]. It has been shown that diastereoselective reduction of the chiral flavon-3-ols by sodium borohydride in methanol yields the *trans*-2,3-dihydroxy compounds, whereas borohydride reduction in dioxan produces the *cis*-isomers [14]; the synthetic procedure confirms the *cis* configuration of the 2,3-hydroxy groups of naturally occurring leucodelphinidins [14].

Basic solid:liquid two-phase conditions with *t*-butyl peroxide and *N*-benzylquininium chloride convert cyclohex-2-enone preferentially into the 2(*S*),3(*S*)-oxirane (20% ee) which, upon purification and treatment with hydrazine, yields (*S*)-cyclohex-2-enol [7]. This reaction contrasts with the direct reduction of cyclohex-2-enone to the *R*-isomer by lithium aluminium hydride in the presence of quinine [20].

Epoxidation of cycloalk-2-enones by oxygen in the presence of 9-*n*-hexylfluorene and a quaternary ammonium salt [17, 21, 22] has been shown to proceed via the intermediate formation of the 9-hydroperoxyfluorene [21]. The catalytic use of cinchoninium salts produces the 2(*S*),3(*S*)-oxiranes in high yields with enantiomeric excesses of up to 63% [17, 21, 22].

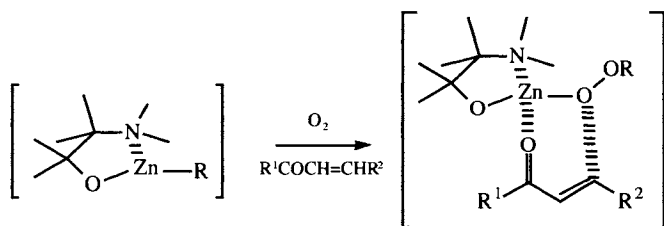
The stepwise formation of epoxides through the reaction of alkenes with sodium hypochlorite with, or without, the isolation of the intermediate chlorohydrin has been subjected to catalysis with *N*-benzylquininium chloride under liquid:liquid two-

phase conditions [3]. Optical purities of only 5–25% were achieved with overall conversions of 65–90%. Higher optical purity was obtained, when the intermediate chlorohydrin was not isolated, and formation of an optically active oxirane from a preformed racemic chlorohydrin appears to be an example of kinetic resolution.

Tetra-*n*-butylammonium hydrogen sulphate facilitates the enantiomeric epoxidation of alkenes by persulphates in the presence of chiral ketones (**10.6.8**). The reaction proceeds via the initial formation of chiral dioxiranes [23].

Asymmetric induction using catalytic amounts of quininium or *N*-methyl-ephedrinium salts for the Darzen's reaction of aldehydes and ketones with phenacyl halides and chloromethylsulphones produces oxiranes of low optical purity [3, 24, 25]. The chiral catalyst appears to have little more effect than non-chiral catalysts (Section 12.1). Similarly, the catalysed reaction of sodium cyanide with α -bromo-ketones produces epoxynitriles of only low optical purity [3]. The claimed 67% ee for the phenyloxirane derived from the reaction of benzaldehyde with trimethylsulphonium iodide under basic conditions [26] in the presence of *N,N*-dimethylephedrinium chloride was later retracted [27]; the product was contaminated with the 2-methyl-3-phenyloxirane from the degradation of the catalyst.

The catalysed reaction of α,β -unsaturated ketones with dialkylzincs and oxygen leads to the formation of chiral acyloxiranes. The initially formed intermediate complex between the chiral β -hydroxyamine and the dialkylzinc (*cf.* Scheme 12.9) is oxidized to the peroxyalkylzinc complex prior to the formation of the chiral oxirane (Scheme 12.13) [28].



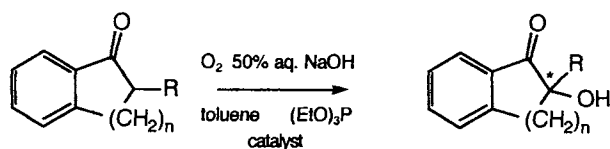
Scheme 12.13

12.5.2 Enantioselective epoxidation of α,β -unsaturated ketones by diethylzinc and oxygen

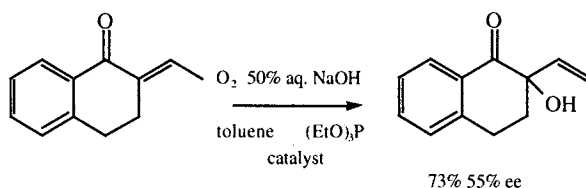
Et₂Zn (1.1M in *n*-C₆H₁₄, 1 ml) is stirred with the (1*R*,2*R*)-*N*-methylpseudonorephedrine (0.43 g, 2.4 mmol) in PhMe (10 ml) under Ar at 0°C for *ca.* 80 min. O₂ is passed through the mixture, which is then stirred for 2.5 h. The mixture is cooled to -78°C and the α,β -unsaturated ketone (1 mmol) in PhMe (2 ml) is added. After stirring the mixture at -78°C for *ca.* 3 h, it is brought to 0°C and the reaction is quenched with aqueous phosphate buffer (pH 7, 8 ml). The organic phase is separated and the aqueous phase is extracted with CH₂Cl₂ (4 × 10 ml). The combined dried (Na₂SO₄) organic solutions are evaporated to yield the (*R,S*)-acyloxirane [e.g. from PhCOCH=CHMe, 96% (85% ee); from PhCOCH=CHPh, 94% (61% ee)].

Hydroxylation of ketones

Phase-transfer catalysed oxidation of ketones with dioxygen under basic conditions in the presence of triethyl phosphite and a cinchonium salt produces α -hydroxyketones (Schemes 12.14 and 12.15, Table 12.9) in good overall yield (~95%) and with a high enantiomeric excess [$>70\%$ ee using *N*-(4-trifluoromethylbenzyl)cinchonium bromide] [29]. Lower asymmetric induction is observed with ephedrinium salts, polymer-supported salts and, surprisingly, by cinchonidinium salts.



Scheme 12.14



Scheme 12.15

TABLE 12.9

Examples of the asymmetric α -hydroxylation of benzocycloalkanones using *N*-(4-trifluoromethylbenzyl)cinchonium bromide

Cycloalkanone (Scheme 12.14)		α -hydroxylated product		
R	<i>n</i>	% yield	ee	configuration
Me	2	95	70	S
Et	2	98	72	S
<i>i</i> -Pr	2	59	77	R
Me	1	94	73	S

12.5.3 Synthesis of chiral α -hydroxyketones

The ketone (1 mmol) in PhMe (10 ml), Et_3PO_3 (0.2 g, 1.2 mmol) and the catalyst (0.05 mmol) are added to aqueous NaOH (50%, 2.5 ml) and O_2 is bubbled through the vigorously stirred solution until all of the ketone is consumed. H_2O (10 ml) is then added and the aqueous phase is separated and extracted with C_6H_6 (2×5 ml). The combined organic solutions are washed sequentially with 10% aqueous HCl, H_2O , and brine, dried (Na_2SO_4), and evaporated. Chromatography from silica yields the α -hydroxyketone.

The oxidation of alkenes with potassium permanganate in the presence of chiral menthylammonium salts has been reported to produce chiral 1,2-diols with low optical purity. It is possible that the products are contaminated with the catalysts or their decomposition products, as no asymmetric induction was observed with (+)-1-phenylethylammonium salts [30].

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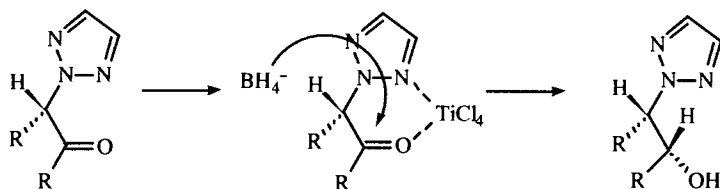
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12.6 REDUCTION

Several early reports of high asymmetric induction during the hydride reduction of ketones under the influence of chiral catalysts [e.g. 1, 2] have been discredited [3–6].

In the later work, low optical activity (<30% ee) was observed for the products [e.g. 5] and the high asymmetric induction of the earlier work was attributed to carry over of the catalyst or chiral degradation derivatives (oxiranes) of the catalysts. Although the reported stereoselective reduction of acetophenone has been discredited, it has been suggested that the use of a chiral solvent, such as menthyl methyl ether, enhances the asymmetric reduction [7]. The veracity of this claim has not been proven.

Other reports of stereoselective borohydride reduction of ketones, using procedures analogous to those described in **11.3.2**, indicate variable and frequently poor asymmetric induction [8–14]. Enhancement of the induced asymmetric reduction by immobilization of the chiral catalyst on montmorillonite [14] has been shown to be insignificant. However, available evidence shows that the more bulky ketones (e.g. 3,3-dimethyl-1-phenyl-propan-1-one) are more likely to be reduced stereospecifically [4, 8, 11, 12] and that, although *N*-dodecyl-*N*-methylephedrinium salts are more effective for asymmetric induction than are *N*-benzyl-*N*-methylephedrinium salts [e.g. 3, 4, 8], there are conflicting opinions as to whether more reliable and effective results are obtained with salts derived from more bulky and rigid cinchona alkaloids. However, the importance of the β -hydroxy group is again apparent in the observed total lack of asymmetric induction, when chiral quaternary salts not possessing such a group are used [3–5, 15, 17]. The configuration of the β -hydroxyl group is generally the more important in stereoselective reduction. Thus, reduction in the presence of quininium [8(*R*),9(*S*)] salts generally leads to the formation of the (*S*)-carbinol, whereas the (*R*)-isomer is obtained with quinidinium [8(*S*),9(*R*)] salts. Similarly, both 1(*R*),2(*S*)- and 1(*R*),2(*S*)-ephedrinium salts generally produce (*R*)-alcohols. However, even these generalizations are not always valid, as the more bulky ketones may be converted into (*R*)-carbinols by quininium borohydride [5] and 3(*R*)-menthyl benzoyl-formate is reduced to 3(*R*)-menthyl (*S*)-mandelate in the presence of 1(*S*),2(*S*)-*N*-dodecyl-*N*-methylephedrinium salts [9]. It is of interest that with catalysts of type **16** (Scheme 12.5) there is no observed asymmetric reduction of 2,2-dimethyl-1-phenylpropan-1-one when the 1(*R*),2(*S*)(*S*)-stereo-isomer is used, but there is 10% ee of the (*R*)-alcohol, when the 1(*R*),2(*S*)(*R*)-isomer is used [12]. It is significant that the products from the electrochemical reduction of acylbenzenes using ephedrinium salts as the supporting electrolyte produce alcohols having the opposite chirality to those obtained by catalysed hydride reduction using the same salts [8]. α -Triazolyl ketones are reduced stereospecifically by tetra-*n*-butylammonium borohydride in the presence of titanium chloride, as shown in Scheme 12.16; the opposite configurational isomers are formed in the absence of the titanium salt [16].



Scheme 12.16

12.6.1 Co-catalytic effect of TiCl_4 on the reduction of α -triazolyl ketones

TiCl_4 (5.69 g, 30 mmol) in CH_2Cl_2 (20 ml) is added to the α -triazolyl ketone (25 mmol) in CH_2Cl_2 (30 ml) at -30°C . The mixture is stirred at room temperature for 30 min, then cooled to -30°C and TBA-BH₄ (3.2 g, 12.5 mmol) in CH_2Cl_2 (20 ml) is added and the mixture is stirred for a further 1 h at room temperature. H_2O (200 ml) is added and the mixture is acidified with aqueous HCl (10%). The aqueous phase is separated and extracted with CH_2Cl_2 (3×25 ml) and the combined organic solutions are washed well with aqueous HCl (10%), aqueous NaHCO_3 (sat. soln) and H_2O , dried (MgSO_4), and evaporated to yield the alcohol.

Borohydride reduction of imines in the presence of ephedrinium salts [8] has produced, at the best, *ca.* 4% ee.

Stereoselective reduction of α,β -unsaturated ketones using lithium aluminium hydride has only been reported in conjunction with the ephedrine bases either in a two-phase system (80–90% yield, ee >70%) or immobilized on a polymer [18, 19].

Reduction of aryl alkyl ketones with moderate to good (ee 30–80%) enantioselectivity has been achieved using trialkoxysilanes in the presence of chiral quininium fluorides (or hydroxides) [20]. Greater selectivities were noted (ee >65%) when tris(trimethylsiloxy)silane was used.

12.6.2 Silane reduction of aryl ketones

The trialkoxysilane (1.5 mmol) is added with stirring at room temperature to the ketone and quininium fluoride (0.02 mmol) in THF (2 ml). When the reaction is complete, as shown by TLC analysis, aqueous sodium hydroxide (3M, 5 ml) is added and the mixture is stirred for a further 12 h at room temperature. The mixture is extracted with Et_2O (3×15 ml) and the extracts are washed well with H_2O , dried (MgSO_4), and evaporated to yield the chiral alcohol.

Hydrogen-bonding between the 3-oxo group of 1,4,4-trisubstituted pyrrolidine-2,3,5-triones and catalytic amounts of cinchonidine controls the stereospecific hydrogenation of the system over $\text{Pt}/\text{Al}_2\text{O}_3$ to yield chiral 3-hydroxy compounds (~100% yield with ee >60) [21]; the nature of the *N*-substituent appears to be the controlling factor for the stereoselectivity with $\text{PhCH}_2 > \text{Et} > n\text{-Bu} > \text{cyclo-C}_6\text{H}_{11}$.

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